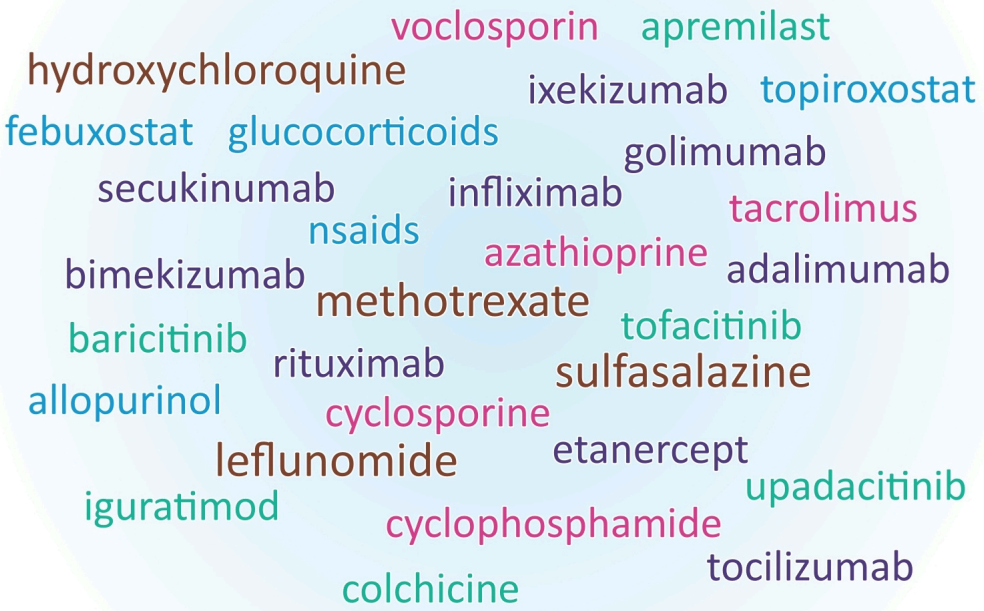
# IRA e-NewsLetter

*an official publication of the Indian Rheumatology Association*

IRA eNL Issue: 2025-3


## Special Issue: September 2025

**Theme** | **Therapeutic Armamentarium in Rheumatology**




**Also features** | **Highlights of All the Issues from 2023 to 2025**


Editor-in-Chief: Vinod Ravindran

Issue Editor: Mohit Goyal

IRA e-NewsLetter
an official publication of the Indian Rheumatology Association

# Special Issue: September 2025

**Issue Editor**
Dr Mohit Goyal
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**Editor-in-Chief**
Dr Vinod Ravindran
Centre for Rheumatology, Calicut

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# IRA President's Message

*Dr Chandrashekara S, Bengaluru*

Dear Members,

I congratulate the Editorial Board of the IRA eNewsLetter on this special issue, "Therapeutic Armamentarium in Rheumatology," which also highlights the issues from 2023 to 2025.

As the current Executive Committee's term ends, I would like to express my sincere gratitude for the privilege of serving you and this esteemed society.

We have put our best efforts into modernising and strengthening our association. We revamped the IRA website, making access to information easier and digitised applications for memberships and grants. We undertook a major outreach effort to update member records, enhancing communication. IRA eConnect program has expanded in both scale and reach, sharing high-quality science from around the world. To support our young rheumatologists, we created SOPs to streamline travel grants and make the IRA SD Deodhar Quiz more organised and inclusive.

Our international engagement has also grown, securing greater Indian representation in APLAR SIGs and increasing our presence at the APLAR Congress. We have relocated the IRA's bank account to a central location in Delhi and secured a locker for easy and secure maintenance of documents.

Several other initiatives have been launched, which may take longer to implement but will ultimately improve the organisation. I am confident the next EC will build on this progress.

Thank you for your unwavering support and dedication to the IRA.

# Message from the Editor-in-Chief

*Dr Vinod Ravindran, Calicut*

Dear esteemed members,

I am delighted to bring this special edition of IRA eNewsLetter to you.

When I commenced my 3-year tenure as the Editor-in-Chief of the IRA eNewsLetter in January 2023, I defined my vision for it as "Be innovative and think of life more and science less" and its mission as "Work together but take the lead and initiatives and execute and try involving local/regional younger colleagues as much as possible".

Looking back, I feel happy and contended that my editorial team of 15 dynamic young colleagues from across India not only delivered that brief, but also went beyond and showcased tremendous innovation and remarkable ingenuity. In the first part of this edition, they have provided an excellent synopsis of each issue they have edited.

The second part of this edition comprises short write-ups on commonly used drugs in our day-to-day practice as "Therapeutic Armamentarium in Rheumatology". I envision it to be a ready and useful reckoner for all of us.

I would like to thank the IRA for giving me this opportunity. I appreciate the constructive feedback and appreciation I have received from you over the years.

Best wishes

# From the Desk of the Executive Editor

*Dr Mohit Goyal, Udaipur*

Dear Seniors and Friends,

As we navigate the complexities of modern rheumatology, it's essential to periodically pause and take stock of the tools at our disposal. This issue of the IRA e-NewsLetter, themed "Therapeutic Armamentarium in Rheumatology," throws light on the diverse drugs that define our practice. It serves not only as a comprehensive guide but also as a reminder of our continuous journey of learning and adaptation.

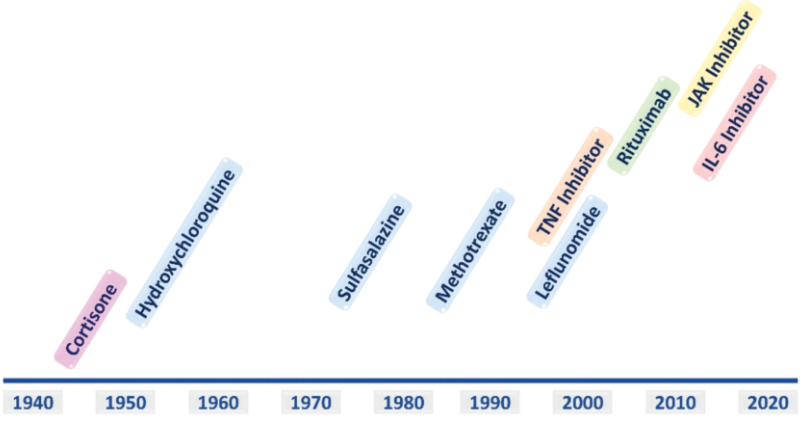
The first section provides highlights of all issues from 2023 to 2025, offering a sneak peek into the themes and the outstanding contributions from IRA members across the country. You can use the scannable codes provided with the highlights of each issue to access the whole issue online.

The heart of this issue, however, lies in its second section, which meticulously details our therapeutic arsenal. The articles on glucocorticoids, non-steroidal anti-inflammatory drugs, and the conventional disease-modifying antirheumatic drugs, offer a blend of foundational principles and contemporary insights. They remind us that while newer biologics and targeted therapies are revolutionising care, the mastery of these conventional drugs remains paramount.

Beyond the pharmacology, our therapeutic decisions must be guided by the unique needs of each patient. This includes not only selecting the right molecule but also meticulously monitoring for adverse effects and ensuring adherence. As our understanding of

these drugs evolves through ongoing research and clinical trials, so too must our approach to patient care. This holistic perspective, blending scientific knowledge with compassionate and personalised application, is the very essence of what makes rheumatology such a challenging and rewarding field.

This section is also a testament to the dynamic and evolving nature of rheumatology. It demonstrates how we strike a balance between the proven efficacy of long-standing treatments and the promise of emerging therapies.




All articles have been subdivided into uniform headings: Pharmacology, Indications in Rheumatology, Dosing and Administration, Adverse Effects and Monitoring, Contraindications and Precautions, and Challenges in Clinical Use and Solutions, to facilitate easy location of the information.

I encourage you to read through it, reflect on the knowledge shared, and consider how you might apply these insights to serve our patients better.

Happy reading!

# IRA eNewsLetter Editorial Board 2023-25

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# IRA eNewsLetter Highlights March 2023 to December 2025

March 2023

# Osteoporosis

*Parthajit Das*

Access Issue Online

This edition of the IRA e-NewsLetter was themed around "Osteoporosis and metabolic bone health" and focused on exploring the history of osteoporosis, diagnostic and therapeutic challenges, complexities of glucocorticoid-induced osteoporosis (GIOP) and an overview of novel therapies.

Osteoporosis-related fractures may have a negative impact on the social, economic and financial health of society. Our sincere effort was to raise awareness of Osteoporosis among treating physicians, implement evidence-based care pathways, and promote safe and effective fracture prevention strategies in the community.

This issue showcases a unique blend of academic achievements, lifelong learning experiences, extracurricular activities, and nurtured hobbies from our fraternity. Prof Sukumar Mukherjee has eloquently narrated "Learning from the mistakes" from his valuable yet challenging experiences in life. Dr Ratan Chandra Kar, a Padmashree awardee, has shared his clinical observations based on his lifetime association with the Jarawa tribe population in the Andaman and Nicobar Islands. Dr Kaushik Chaudhuri has nicely elucidated the history of Osteoporosis in his impeccable linguistic style. Dr Puneet Mashru has discussed the pitfalls of DXA interpretation. Dr V Krishnamurthy Sir has shared his practical viewpoints and experiences depicting the challenges related to combination and sequential maintenance

therapies in Osteoporosis. Dr Ambrish Mithal has aptly deliberated his expert insights on the recent advances in the management of GIOP. Dr Sakir Ahmed, Dr Dhrubojyoti Sharma, and Dr Arghya Chattopadhyay have discussed the most impactful papers in the field of basic sciences and clinical sciences in paediatric and adult rheumatology. Dr Durga Prasanna Misra has discussed the implications of predatory publishing and deceitful practices in scientific writing. Dr Pradip Joshi and Dr Sunil Malvidi have shared their skills with thrilling wildlife photographs that deserve appreciation. Dr Debaditya Roy has designed the quiz with great enthusiasm.

We hope this issue motivates you to appreciate not only the science but also the romance and passion in the lives of scientists.

June 2023

# Treat-To-Target

*Arun Kumar Kedia*

Access Issue Online

The June 2023 issue underpins the importance of the treat-to-target approach in rheumatology. With a better understanding of the molecular pathogenesis of various rheumatic diseases and the subsequent development of targeted biologics and small molecules, remission has become more achievable. The lessons learnt from the success of targeted management of chronic cardiometabolic diseases paved the way for a similar approach, defining a target and then achieving it through frequent assessments, judicious adjustments of drugs, and a prudent involvement of patients in managing the disease. It has been more than a decade since this approach has been well accepted globally. However, numerous practical challenges, both disease-related and patient-related factors, pose difficulties in implementing the strategy. The heterogeneous presentation of Lupus has been highlighted as an example of these challenges.

The issue also highlights the hard work and perseverance of Dr AN Malaviya in laying the foundation of Rheumatology at the All India Institute of Medical Sciences, New Delhi. In an inspirational interview, he also summarised how rheumatology developed in India and how the key leaders contributed. We gained various insights from Dr Paramjeet Singh on the challenges of practising rheumatology in the Himalayan region, exemplifying the quote: "Where there's a will, there's a way." A

fascinating inclusion in this edition was valuable advice from our colleague, Dr Suresh Adimulam, on how to establish a stand-alone rheumatology setup in India, focusing on essentials, sound financial planning, and the need for interdepartmental collaboration for referrals. The Quarter in Review section updated readers on recent interesting developments through summaries of important studies under the various sections of Basic Science, Clinical, and Paediatric Rheumatology.

Our readers were also made to exercise their knowledge and memory through some Quiz questions in the form of MCQs and some interesting clinical pictures.

Lastly, all work and no play makes Jack a dull boy. To add colour to life, the pleasures of completing a marathon and the adventure of mountain biking were highlighted to inspire our readers to indulge in physical activity beyond the clinic.

The theme, 'Treat to Target,' is not a new concept. Still, our contributors have provided an excellent explanation of the concept's evolution, the need for it, and the challenges we face in implementing this strategy. It reminds us again of the famous 1963 song by The Essex, "Easier Said Than Done."

September 2023

# Psoriatic Arthritis

*Mohit Goyal*

Access Issue Online

The issue with the theme of Psoriatic Arthritis encompasses recent advancements, as well as certain less frequently discussed aspects of the disease. The first write-up by Dr Bimlesh Dhar Pandey discusses strategies for personalising treatment and examines the advantages and disadvantages of various drugs in specific clinical scenarios. The article by Dr Ashish Jacob Mathew discusses the unmet needs and ponders what the future holds for treatment options in psoriatic arthritis. Dr Pravin Patil discusses India-specific challenges in managing psoriatic arthritis. Dr Rajiv Sekhri, a senior dermatologist, provides a quick guide on recognising uncommon forms of psoriasis for rheumatologists.

Two articles add different perspectives to the issue. First is an interview with Dr Vikas Agarwal, a former Editor-in-Chief of the Indian Journal of Rheumatology, on the challenges of editing a medical journal. The second is a patient's perspective, which discusses the rewards of meticulously adhering to treatment and also includes some small but critical lessons for caregivers.

The Quarter in Review section showcases the most impactful basic and clinical science and paediatric rheumatology research works published in the preceding three months.

Another highlight of the issue is the article in the Young Rheumatologist Corner, which, through three curated cases, teaches why history taking, clinical examination and careful

review of records remain indispensable, despite the invent of any and every new investigation and modality.

A novel addition to the format is the rheumatology crossword, for which Dr Suma Balan picked up her magic wand and threw in some poetic clues. You can go to the article in the issue and fill in the crossword on your mobiles or computers and check how many you can get!

The Image of the Quarter section features two intriguing cases by Drs Akhil Goel and Satyam Bhatt. Please try to solve and then check how close you were by clicking on "View Answer". The "Life beyond..." section features Dr Suvrat Arya's passion for music and its place in his life. It also features the fascinating birding journey of ace photographer Dr Arun Hegde.

You can scan the accompanying QR code to access the whole issue online.

December 2023

# Artificial Intelligence in Rheumatology

*Keerthi Talari Bommakanti*

Access Issue Online

The December 2023 edition of the IRA e-NewsLetter explored the theme "Artificial Intelligence (AI) in Rheumatology". As the Executive Editor for this issue, I had the privilege of curating a range of perspectives that demystified AI and illustrated its potential to transform clinical practice, research, and education in rheumatology.

This theme was chosen to reflect the rising tide of digital transformation in healthcare and to bring AI into sharper focus for the practising Indian rheumatologist. While AI applications have been emerging globally, their relevance and readiness for clinical settings in healthcare require contextual discussion-something this issue aims to provide.

The content spanned core concepts, including machine learning, deep learning, natural language processing, and multimodal AI. We showcased how these tools are already being applied in rheumatology-from image recognition and automated scoring systems to disease subtyping and predictive modelling. Highlights included articles on large language models, such as ChatGPT, for academic writing and patient engagement, as well as expert commentary on ethics in AI, including algorithmic bias, data quality, and AI governance.

What made this issue unique was its practical and accessible tone. A glossary of AI terms helped break down

technical barriers, making it easier for readers to engage meaningfully with AI.

In addition to the thematic content, the issue featured powerful human stories and community voices. Dr Kavitha MM's perspective piece, "Empowered Rheumatologists - Women Leading the Way," brought attention to gender leadership in rheumatology. Interviews with Dr Prasandeep Rath (on early career challenges) and global voices, such as Drs Shabina Habibi (UK) and Chanakya Kodishala (USA), regarding career opportunities overseas added depth and diversity to the issue's narrative. Rounding off the issue were vibrant updates from IRACON 2025 in Hyderabad, capturing the scientific highlights from our annual conference.

This issue stands at the intersection of innovation and introspection-a forward-looking edition that bridges technology and clinical insights.

March 2024

# Spondyloarthritis

*Himanshu Pathak*

Access Issue Online

The IRA March 2024 eNewsLetter provides a comprehensive, multidimensional exploration of axial spondyloarthritis (axSpA) and related rheumatology topics. It includes clinical science articles, expert perspectives, epidemiological reviews, patient support group initiatives, and lifestyle columns. The central theme is axSpA, covered through diverse lenses, ranging from diagnostic delays in India to the recognition of inflammatory back pain, differences between juvenile and adult SpA, sex disparities in diagnosis and response, and patient advocacy work. A variety of academic updates (e.g. reviews of key studies in clinical and basic science) and personal reflections (e.g. fitness, reading habits, and work-life balance) enrich this issue.

The focus on axSpA is highly relevant, particularly in India, where the disease burden is underrecognized and often misdiagnosed due to poor awareness at both the primary care and patient levels. With axSpA primarily affecting young adults in their productive years, this theme is critical from both a public health and a clinical standpoint. It also aligns well with the broader goals of the Indian Rheumatology Association, which aim to enhance awareness on early diagnosis and holistic management of rheumatic diseases.

This issue adds a real-world Indian context to the global discourse on rheumatology. Key novel insights include: the unique challenges in diagnosing female axSpA, highlighting the

subtle clinical cues that are often missed in routine care; the contrast between juvenile and adult SpA in terms of presentation, classification, and transition of care; public health and epidemiological perspectives of senior Indian rheumatologists emphasising the need for local data and tailored care pathways; grassroots initiatives by patient support groups such as ASWS and Antardhwani that are crucial in improving patient education and access to therapy; updates on emerging therapies (e.g. bimekizumab in PsA, tofacitinib in JDM) and cutting-edge basic science (e.g. exosomal biomarkers in AS), which expand the reader's horizon beyond conventional clinical practice.

This issue successfully blends science, clinical practice, personal reflection, and advocacy. This serves as an excellent model for a holistic academic communication vehicle tailored to Indian rheumatology professionals.

June 2024

# Holistic Health in Rheumatology with a Focus on Comorbidities

*Pankti Mehta*

Access Issue Online

The June 2024 edition of the IRA e-NewsLetter brings a timely and essential focus on "Holistic Health in Rheumatology with a focus on comorbidities." As the field of rheumatology advances, the lens through which we view our patients must also evolve. With improved therapeutic outcomes and longer life expectancies, the burden of comorbidities in rheumatic diseases has taken centre stage. This issue reflects the shifting paradigm, from managing inflammation alone to embracing comprehensive patient care that integrates physical, metabolic, and psychosocial health.

The choice of the theme was deliberate. Chronic conditions such as hypertension, diabetes, and cardiovascular disease are not merely co-passengers in rheumatic illnesses but influence disease activity, treatment response, and overall quality of life. As rheumatologists, our expanding role includes monitoring modifiable risk factors and creating frameworks that support anticipation, prevention, and integrated management of these co-existing conditions.

The opening section examines the historical recognition of comorbidities in rheumatic disease, as well as the mechanistic insights that inform routine clinical practice. Through a blend of narrative review, evidence-based summaries, and personal approaches, it offers readers practical pathways to manage patients better holistically.

This issue features exclusive interviews with two renowned experts in the field of rheumatology. Dr Amita Aggarwal shares invaluable guidance on how young clinicians can choose and nurture research interests, while Dr Mike Putman offers an insightful take on interpreting clinical trials.

The Quarterly Review section brings together top articles from the basic sciences, clinical sciences, and paediatric rheumatology, helping readers stay up-to-date with recent developments. In parallel, visual case challenges and curated quizzes invite readers to test their knowledge and engage interactively with the content.

Adding a personal dimension to the newsletter, the "Life Beyond" section celebrates life outside medicine. From culinary explorations to the fine art of pen collecting, contributors open a window into their hobbies, reminding us that holistic health encompasses not only physical well-being but also nourishing the soul.

What's new in this edition is not just the theme, but the emphasis on integration. The issue weaves together patient care, research, clinical education, and personal wellness, offering a truly holistic perspective on what it means to be a modern rheumatologist.

We hope this issue inspires you to look beyond inflammation and toward the whole person behind each diagnosis.

August 2024

# Perspectives and Nostalgia in Rheumatology

*Kushagra Gupta*

Access Issue Online

The August 24 issue of the IRA e-Newsletter is curated to address aspects of our clinical practice that are often overlooked. This issue covers essential life skills that are not taught in any book or college but are important for practising medicine in the real world. Most of us acquire this knowledge by trial and error over the years of practice. An objective look at these things helps to put our thoughts into a better perspective.

Some new and noteworthy practical aspects covered in the issue:

Behavioural economics: Despite optimal treatment strategies, patient outcomes vary. Emotions and past experiences dictate real-world patient behaviour. Understanding the psychology of our patients can help anticipate human errors and improve patient compliance and follow-up in practice. This is a must-read article for all practising clinicians!

Fast and Slow thinking: Diagnosing requires critical thinking on our part. Emergency management relies on fast thinking to make quick decisions. While impressive, it is prone to errors. On the other hand, slow thinking, which is more reliable, is required when dealing with a complicated clinical case that necessitates ruling out various possibilities. Understanding the difference can improve practice.

Guide to Electronic Record Keeping in Practice: We have all likely considered incorporating electronic record keeping into our practices to stay current with the changing times. But due to a lack of knowledge regarding the options or general apprehension, we don't. Our article provides an update on the various available modalities, their pros and cons, and offers guidance on selecting the best option for your practice.

Reflection on Older DMARDs: In the era of Biologics, our article discusses older DMARDs, such as azathioprine, cyclosporine, and chronic low-dose glucocorticoids, from the perspective of one of our seasoned colleagues and how they might still be relevant in the management of rheumatoid arthritis, especially when managing a challenging case in resource-constrained settings.

Since it can't be all work, we need to balance this with some fun too. So, our articles with their trivia-based approach will help you take the edge off: Autoimmunity and Memes; Evolutionary link between plague and FMF; How the brilliant deductive skills of our favourite sleuth (Sherlock Holmes) were inspired by the way doctors diagnose patients; clinico-pathological conferences and their origin; a look at rheumatology practice 100 years ago; initial challenges in setting up the department at SGPGI, Lucknow; spot the diagnosis to stimulate those grey cells; a look at the extracurricular talents of our young rheumatology professionals.

We hope you find this issue to be inspiring and stimulating. Happy Reading!

October 2024

# Lupus

*Sunitha Kayidhi*

Access Issue Online

Lupus is a systemic autoimmune disease that primarily affects women in their young and middle age. Its complexity, heterogeneity, and the challenges associated with diagnosis and management make it an intriguing subject to study. In recent years, a paradigm shift has occurred in lupus research. As rheumatologists, we need to gain a deeper understanding of this disease to improve treatment outcomes. Therefore, this theme was chosen for this issue.

This issue begins with a summary of nearly 12 centuries of lupus history, covering everything from cutaneous lupus to systemic forms, the evolution of diagnostics, changes in classification criteria, and advancements in therapies. Following this overview, the issue delves deeply into the immunopathogenesis of lupus. Despite significant improvements in diagnosing and managing lupus over the past two decades, some patients still do not respond well to treatment. Next, the issue explores the causes and management of difficult-to-treat lupus nephritis. This section is followed by a discussion of newer targeted treatment options for lupus, highlighting ongoing clinical research in emerging therapies.

In the interview segment, we invited both global and Indian lupus experts to share their insights on the challenges faced by lupus patients regarding access to care and to suggest potential solutions. It's essential to recognise that lupus affects each

person differently, and the disease courses vary. Therefore, patients need to have a certain degree of understanding of the disease to communicate their experiences and seek appropriate treatment. The final section of this theme highlights Lupus Trust India, a patient advocacy group that supports and educates lupus patients while addressing their emotional and psychological needs.

I sincerely thank all the authors for their contributions and efforts. I extend my gratitude to Dr Vinod Ravindran and the editorial board for the support.

December 2024

# The Intersection of Malignancy and Rheumatology

Kavitha MM

Access Issue Online

The intersection of malignancy and rheumatology represents a growing clinical challenge due to the complex and bidirectional relationships between cancer and rheumatic diseases. This interplay manifests in several ways: immunosuppressive therapy and cancer risk, paraneoplastic rheumatic syndromes and temporal association, increased cancer risk in autoimmune rheumatic diseases, and immune system interactions and cancer immunotherapy.

DMARDs decrease tumour surveillance, complicating risk assessment. JAK inhibitors have transformed the treatment of rheumatic diseases but may increase the risk of malignancy by impairing immune surveillance, particularly in NK cells. Evidence is mixed, with risk influenced by patient factors and treatment duration.

Rheumatic diseases and malignancies share a bidirectional link, with diseases like Sjögren's syndrome showing a 13 to 15-fold lymphoma risk. Specific cancers vary by disease (e.g., lung, hematologic, breast). Vigilant cancer screening, especially in patients with systemic signs or refractory disease, is crucial. Indian guidelines tailored to local needs are needed.

Immune checkpoint inhibitors enhance anti-tumour immunity by blocking CTLA-4 and PD-1/PD-L1 pathways. They can cause rheumatic immune-related adverse events like arthritis and myositis, differing from classic rheumatic diseases. Treatment ranges from NSAIDs to biologics, with careful

management of ICI therapy, even in patients with pre-existing rheumatic conditions.

Dr Binoy Paul reflects on how gout is still a common rheumatological illness but is treated inadequately, especially in India, where prevalence is higher than expected. Advances such as ultrasound and DECT enhance diagnosis. He felt that Indian patients show distinct patterns.

A highlight of this issue is an interview with an eminent Medical Doctor turned scientist - an expert in nanomedicine, Dr Aravind Kumar Rengan. The relevance of nanomedicine to rheumatology, particularly in early diagnosis, targeted drug delivery, real-time monitoring, enhanced permeation, and reduction of systemic side effects, suggests that the future is indeed bright. This interview sparked thoughts about potential collaborations.

Dr Sushanth Shinde, a TEDx speaker, reflected on the changing landscape of Medical Education, making us ask a critical question: Should we celebrate it nostalgically or view it with concern? The limitations of exam-centric learning and the challenges and opportunities of online education have been discussed. He also addresses the missing ends of medical education and training - empathy, financial literacy and mental health.

Dr Sriram reflects on doctors' limited engagement in politics, despite the deep connection between public health and policy. Medical education rarely encourages political involvement, creating a leadership vacuum in healthcare advocacy. The author urges doctors to embrace political roles, balancing clinical duties with active participation to influence health policies and societal well-being.

March 2025

# Musculoskeletal Ultrasound in Rheumatology

*Vikramraj K Jain & Gayatri Ekbote*

Access Issue Online

The March 2025 edition of the IRA e-NewsLetter focused on a transformative and timely theme: Musculoskeletal Ultrasound (MSK-US) in Rheumatology. Musculoskeletal ultrasound (MSK-US) has become an indispensable tool in rheumatology, providing real-time, point-of-care imaging that enhances diagnostic accuracy and facilitates monitoring of treatment response, as well as guiding interventions. Recognising its growing significance and the need for nuanced discussions around it, we dedicated this issue to exploring MSK-US from multiple vantage points- clinical, technological, medicolegal, and educational.

The issue included in-depth articles that move beyond the routine, highlighting lesser-known applications such as large vessel imaging and ultrasound-guided interventions. A fascinating piece discussed the current status of artificial intelligence in MSK-US, its potential benefits and its challenges & limitations.

Recognising the growing importance of MSK-US training, the issue included a practical guide by Dr Joe Thomas for young rheumatologists, covering the different MSK-USG training programs, how to choose one, and some valuable resources to build proficiency. For training in MSK-US, access to an ultrasound machine regularly is an absolute must. An informative article on purchasing a machine for MSK-US, tailored to your practice, expertise, and budget, including probe details and costs, was included to aid in the decision.

MSK-US also presents several practical challenges in India, where access to formal training and clarity on medico-legal responsibility remain limited. Rheumatologists who want to use MSK-US often navigate uncharted waters. In an exclusive interview, Dr Lt. Gen. Ved Chaturvedi shared valuable insights into the legal frameworks, interdisciplinary boundaries, and best practices for integrating MSK-US into routine rheumatology care.

A special spotlight was cast on fibromyalgia, a frequently neglected condition despite its profound impact on patients' quality of life. In a candid conversation, Dr BG Dharmanand discussed real-world strategies to approach fibromyalgia, including medications, exercises and teamwork to deal with this disease that is often frustrating to manage.

As always, our Quarterly Basic and Clinical Science Reviews distilled the most impactful recent research into actionable insights. The popular Image Challenge and Ultimate Rheumatology Quiz returned, engaging readers through interactive learning and diagnostic skill-building.

The "Life Beyond Rheumatology" column took a soulful turn, reflecting on life through the lenses of trekking and painting. These personal narratives served as a gentle reminder to pause, rejuvenate, and find joy in pursuits beyond the clinic.

This edition stood out by offering practical, India-specific insights into the evolving landscape of MSK-US in rheumatology. This transformed the theme of MSK-US from a technical discussion into a valuable, real-world resource, making it especially relevant for rheumatologists in India who seek to integrate ultrasound into their clinical workflow.

June 2025

# Connective tissue disease-associated interstitial lung disease

*Akshat Pandey & Sham Santhanam*

Access Issue Online

We chose connective tissue disease-associated interstitial lung disease (CTD-ILD) as the theme for the June 2025 issue of the IRA e-newsletter. In our daily clinical practice, we frequently see patients with CTD-ILD. Managing CTD-ILD presents various challenges, such as early diagnosis, risk stratification, selecting appropriate drugs to control ILD alongside other extrapulmonary manifestations, dealing with treatment resistance, monitoring difficulties, and the necessity for multidisciplinary care. We chose this subject due to its practical relevance and the unmet needs in managing CTD-ILD. The management of CTD-ILD poses a challenge for both patients and physicians.

The articles in the issue ranged from practical aspects of CTD-ILD management and a perspective on systemic sclerosis-interstitial lung disease, to a rheumatologist's journey providing hematopoietic stem cell transplantation (HSCT) for systemic sclerosis, and an inspiring story of a patient with CTD-ILD who underwent HSCT.

In the article on Interstitial Pneumonia with Autoimmune Features (IPAF), Dr C Saranya emphasises the role of rheumatologists in diagnosing IPAF, considering their clinical expertise in identifying subtle signs and interpreting serological markers in the relevant clinical context. Dr CB Mithun discusses RA-ILD, highlighting the challenges of managing a patient with both active arthritis and progressive lung disease. He

emphasises the relative safety of methotrexate in RA-ILD and its continuation in patients with stable lung disease. He discusses the utility of rituximab for arthritis and ILD, as well as other biologic agents, such as abatacept and tocilizumab, which are considered safe alternatives. The following article by Dr Rajesh Kanumuri addresses the future of rheumatic disease management, specifically focusing on the role of precision medicine in the management of CTD-ILD. He discusses the requirements for this approach and the concept of 'treatable traits.' Lastly, the role of biomarkers and other technologies in diagnosing CTD-ILD, along with the challenges associated with their implementation, is addressed. When all medical options fail and lung disease progresses, we look to the definitive treatment: lung transplantation (LT). Dr Srinivas Rajagopala discusses the indications, contraindications, pre-transplant considerations, and outcomes of LT in CTD-ILD.

The most challenging disease among CTD-ILD is managing ILD in patients with systemic sclerosis. Dr Solanki, a senior expert, discusses the challenges in diagnosis and monitoring, treatment regimens, emerging treatment options, and the role of multidisciplinary care in managing systemic sclerosis-associated interstitial lung disease. Other highlights include the article by Dr Naval Mendiratta on his journey performing 15 hematopoietic stem cell transplants (HSCTs) in patients with systemic sclerosis in the Indian setting, which covers his inspiration, challenges, and plans. It is followed by the journey of Miss Gowthami, who shares her struggles, her fight against the disease, her transformation after undergoing HSCT, and the positive impact she has had on others.

December 2025

# Pulmonary Hypertension in Connective Tissue Disorders

*Upendra Rathore & Madhuri HR*

Access Issue Online

The December 2025 issue of the IRA eNewsLetter will be the final issue of the editorial board's tenure, led by Dr Vinod Ravindran. As the 40th national conference, IRACON 2025, will be held in October this year, this issue will cover the highlights of the conference, focusing on the key take-home messages from the talks.

In continuation of the theme of connective tissue disease-associated interstitial lung disease (CTD-ILD), as presented in the June 2025 issue, the December issue will focus on Pulmonary Hypertension (PH) in CTDs.

Pulmonary arterial hypertension is a serious and potentially life-threatening complication of various CTDs. The theme has been chosen to highlight the growing need for early detection and multidisciplinary management of CTD-PAH. This issue will highlight approaches and treatment preferences, as well as strategies for improving the survival and quality of life for patients. Raising awareness amongst our readers is a goal. The risk factors for developing pulmonary hypertension in different CTDs will be explored. An in-depth understanding of the pathogenesis of PH in CTDs will be presented. Newer evaluation techniques and biomarkers will be delved into, and the screening and diagnostic algorithms will be discussed. The various treatment strategies, including the role of rehabilitation, will be

addressed. The landmark trials in the management of CTD-ILD will be summarised.

Interviews with eminent clinicians on managing stress and preventing burnout will guide younger colleagues in their professional journey, while images of the quarter and a quiz will engage our readers. The section on life beyond will reveal the varied talents of our colleagues.

IRACON 2025, the annual conference of the IRA, will be held in the vibrant city of New Delhi in October. This year's theme, "Innovative ideas, Collaborative wisdom and Compassionate care," highlights the triad essential to advancing rheumatology. The scientific program will showcase cutting-edge research and will be an academic feast. The highlights of the conference will be summarised in the December 2025 issue.

# Therapeutic Armamentarium in Rheumatology

# GLUCOCORTICOIDS

*Kushagra Gupta*

Glucocorticoids (GCs) are the primary treatment for many autoimmune diseases. Glucocorticoids are effective in controlling inflammation in the short term; however, long-term side effects preclude their chronic use, especially when administered in high doses. The article aims to provide the latest, up-to-date information regarding the use of GCs in rheumatic diseases.

## Pharmacology

Glucocorticoids reduce the activation, proliferation, differentiation, and survival of various inflammatory cells, as well as the associated release of cytokines. They exert their anti-inflammatory action through genomic and non-genomic mechanisms.

Genomic mechanisms are mediated via cytosolic GC receptors, which bind with GCs, translocate into the nucleus, and influence gene expression by binding to specific sites on the DNA. This results in increased transcription of regulatory proteins (transactivation) or suppressed transcription of pro-inflammatory proteins (transrepression), causing anti-inflammatory effects.

Non-genomic mechanisms work extremely fast (within seconds or minutes). Their understanding requires further research, but the interaction of GCs with membrane-bound receptors, the release of proteins from the cytosolic GC receptor multiprotein complex, and the interaction of GCs with cellular membranes at high concentrations are some of the mechanisms

behind this action. At very high doses, the non-genomic effects of GCs become prominent, which are responsible for providing immediate relief and improving the patient's clinical status. These effects are most marked for methylprednisolone (3 times more), due to which it is the preferred drug for giving pulse therapy in life-threatening situations.

## Indications in Rheumatology

GCs have multiple indications in rheumatology, ranging from pain relief in arthritides and disease-modifying effects in nerve entrapment syndromes to life-saving immunosuppression in connective tissue diseases, vasculitis, and myositis.

***Indications of Glucocorticoids in Rheumatic Diseases***

| Glucocorticoid Route/Dose | Indications |
|---|---|
| Intra-articular/Intra-lesional | Mono and Oligoarthritis<br>Bursitis<br>Tenosynovitis<br>Carpal Tunnel Syndrome |
| Low - Moderate dose<br>(Low < 7.5mg)<br>(Moderate 7.5-30mg) | Rheumatoid Arthritis<br>Gout<br>Calcium Pyrophosphate Deposition Disease<br>Sjögren Syndrome<br>Mixed connective tissue disease<br>Polymyalgia Rheumatica<br>Interstitial Lung Disease |
| High - Very high dose<br>(High >30mg)<br>(Very high >100mg) | Systemic Lupus Erythematosus<br>Vasculitis<br>Idiopathic Inflammatory Myopathy<br>Adult-onset Stills diseases |
| Pulse therapy<br>(>250mg) | Vasculitis<br>Idiopathic Inflammatory Myopathy<br>Systemic Lupus Erythematosus<br>Macrophage activation syndrome |

## Dosing and Administration

Glucocorticoids in their free form are insoluble in water and can be administered as tablets. Tablets have fast absorption, i.e., within 30 mins, with a very high bioavailability. GC esters (methylprednisolone acetate) are lipid-soluble and are ideal for intramuscular or intra-articular use. GC salts (methylprednisolone succinate), on the other hand, are water-soluble and can be administered intravenously.

Since cortisol is a naturally occurring hormone in our body, its circadian rhythm is essential for basic metabolic processes. Serum cortisol levels peak about half an hour after waking up. To minimise the adverse effects of GCs, they should be administered early in the morning, as close as possible to the endogenous peak levels. A proton pump inhibitor may be co-administered in those who experience gastritis with this early morning dosing. This causes minimal disruption to the circadian rhythm and minimises adverse effects. Also, the pro-inflammatory cytokines (responsible for early morning stiffness), which also peak in early morning, are better countered when GCs are administered in the early morning hours.

Administration regimes for GCs depend on the indication for which it is being given. For inflammatory arthritis such as rheumatoid arthritis (RA), glucocorticoids are mainly used as bridging therapy until the effect of disease-modifying anti-rheumatic drugs (DMARDs) sets in; for systemic diseases such as systemic lupus erythematosus (SLE) or vasculitis, initial high doses followed by long-term low-dose glucocorticoid therapy may be necessary to prevent relapses. Since a state of relative hypocortisolism exists in chronic inflammatory conditions, a low dose of glucocorticoid is considered a physiological replacement dose in rheumatic diseases.

### *Comparison of Different Glucocorticoids*

| Glucocorticoids | Dose equivalent to 5 mg prednisolone (in mg) | Relative mineralocorticoid activity | Biological Half-life (hours) | Maternal to foetal blood concentration |
|---|---|---|---|---|
| Hydrocortisone | 20 | 1 | 8–12 | 6:1 |
| Prednisolone | 5 | 0.6 | 18–36 | 10:1 |
| Methylprednisolone | 4 | 0.5 | 18–36 | _ |
| Triamcinolone | 4 | 0 | 18–36 | _ |
| Deflazacort* | 6 | 0 | 18–36 | _ |
| Dexamethasone | 0.75 | 0 | 36–54 | 3:1 |

**Markham A et al. Deflazacort. A review of its pharmacological properties and therapeutic efficacy. Drugs. 1995;50(2):317-33*

## Adverse Effects and Monitoring

The risk and spectrum of adverse effects appear to depend on the dose and duration of GCs. The incidence of toxicity is low when used for short durations. Most toxicities are reversible.

### *Adverse Events Seen with Glucocorticoid Use*

| Organ systems | Potentially serious adverse events (mostly with high doses) | Common adverse effects (Low or High dose) | |
|---|---|---|---|
| | | Less likely to occur | Highly likely to occur with long-term use |
| **General** | • Increased risk of infection | | • Weight gain |
| **Cardiovascular** | • Fluid retention (aggravates heart failure)<br>• Myocardial rupture | • Bradycardia<br>• Hypokalaemia | • Atherosclerosis |
| **Neurological** | • Psychosis | • Myopathy (more with chronic GC use, worse with fluorinated GCs)<br>• Insomnia<br>• Paraesthesia<br>• Increased intracranial pressure | |

| | | | |
|---|---|---|---|
| **Gastrointestinal** | • GI perforation (pre-existing diverticulosis, peptic ulcer disease, bowel anastomosis) | • Peptic ulcer disease (risk becomes 3 times with concomitant NSAIDs) | • Increased appetite |
| **Haematological** | | | • Bruising<br>• Petechiae |
| **Eye** | • Glaucoma (mostly with topical GCs) | • Central serous retinopathy | • Cataract |
| **Endocrine** | • New-onset Diabetes | • Cushingoid features (25%)<br>• Growth retardation in children (less if dose <0.5mg/kg)<br>• Menstrual irregularities (decreased LH and FSH)<br>• Hirsutism | • Hyperglycaemia<br>• Osteoporosis<br>• Adrenal suppression<br>• Dyslipidaemia |
| **Skin** | | • Atrophic striae<br>• Acne vulgaris<br>• Delayed wound healing | • Skin atrophy |
| **Skeletal** | • Fragility fractures<br>• Avascular necrosis | | |

*GC: glucocorticoids; GI: gastrointestinal; NSAIDs: non-steroidal anti-inflammatory drugs; FSH: follicle-stimulating hormone; LH: luteinising hormone*

## Monitoring

- Blood pressure and weight should be monitored at each visit.
- Periodic blood sugar and lipid profile monitoring.
- Bone mineral density estimation
  - Baseline before starting long-term glucocorticoid therapy (>3 months).
  - Fracture risk (FRAX) assessment every 1-3 years (off treatment) or every 2-3 years (on treatment) for osteoporosis.
- For occult blood loss in patients with persistently low haemoglobin.

- Growth monitoring in paediatric patients (as per WHO/IAP percentile charts).
- Hypothalamic Pituitary Adrenal axis suppression (adrenocorticotropic hormone stimulation test)
  - Routine screening is not recommended.
  - Random serum cortisol levels below 18 mcg/dl in patients with clinical suspicion of adrenal insufficiency warrant screening.
  - Serum cortisol levels < 3 mcg/dl confirm adrenal insufficiency.
- Ocular screening (no definite consensus)
  - For Cataract - After 5 years of regular use or when symptomatic.
  - For Glaucoma - Screening in patients with myopia, diabetes or a family history of glaucoma.

## Contraindications and Precautions

- Pregnancy - Use the minimal possible dose. Prednisolone is the drug of choice for maternal indications, and dexamethasone for foetal indications.
- Breastfeeding - Doses of up to 20 mg of prednisolone are safe. When using higher doses, avoid nursing for 4 hours after taking the tablet.
- Surgical patients
  - Minor/Elective surgery (Dental, Cataract, Joint Replacement) - Continue the same dose of GCs or increase the dose slightly for 1 week for patients on long-term low-dose therapy.
  - Major surgery - Switch to hydrocortisone 100 mg 8 hourly until oral medicines can be resumed and tapered to the previous stable dose.
- Gastrointestinal disease - Risk of perforation in patients with diverticulosis, latent peptic ulcer, and recent intestinal anastomosis.

- Cardiac patients - Worsening of disease due to fluid retention and risk for myocardial rupture.
- Diabetes - Risk of Hyperglycaemia.
- Cirrhosis - GC effects may be enhanced due to decreased hepatic clearance.
- Glaucoma - Increased intraocular pressure can lead to blindness.
- Myasthenia gravis - Transient worsening of disease.

## Challenges in Clinical Use and Solutions

***Challenge 1:*** GCs, when administered in high doses, can sometimes cause sodium retention and generalised puffiness, especially on the face. This can be worrisome for some patients, especially young females.

***Solution:*** Using GC preparations with low mineralocorticoid activity, restricting salt intake, and administering the tablet early in the morning can help alleviate this problem.

***Challenge 2:*** Administering GC tablets as bridging therapy carries a risk of the patient abusing this drug. Often, the patients end up taking only the GC tablet (due to fast relief and low pill burden) and skip all other DMARDs and eventually develop dependence.

***Solution:*** Administering bridging GCs as weekly intramuscular injections minimises the risk of abuse by the patient.

***Challenge 3:*** GC intake can sometimes be associated with insomnia.

***Solution:*** Administering GCs in the early morning hours (on waking up) can help solve the problem without the need for sedatives.

# NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

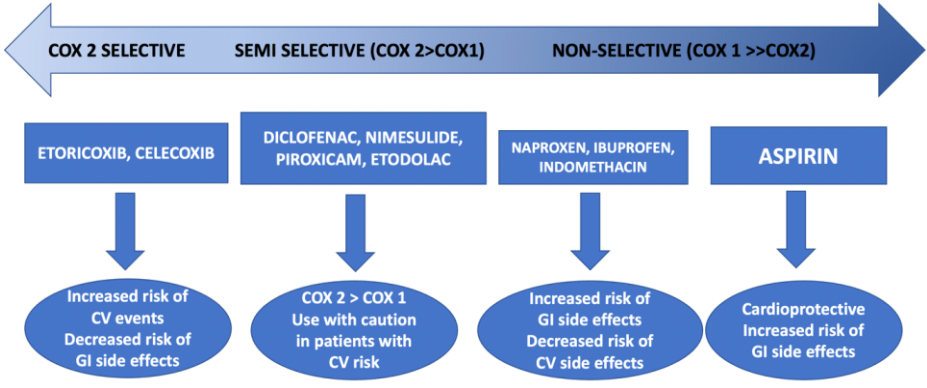
*Sham Santhanam*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs commonly used in our daily practice for analgesics, antipyretics and anti-inflammatory purposes. There are more than 20 different molecules available, of which at least around 10 molecules are commonly used in our setting. NSAIDs are classified based on their chemical properties, isoenzyme selectivity, dosing, and other characteristics, but the common factor is the inhibition of prostaglandin production by blocking the enzyme cyclooxygenase. Being a commonly used drug, one should be aware of its indications, contraindications, adverse events, dosing and other drug-related factors so that they are used appropriately. The choice of NSAID depends on the clinical indication, age, and comorbidities of the individual patient. However, the response to an NSAID may differ between patients, and the response to different NSAIDs in the same patient may also vary.

## Pharmacology

The actions of NSAIDs are mediated by inhibition of prostanoid biosynthesis. Arachidonic acid is a phospholipid ester present in the cell membrane, and prostanoids are synthesised from it, with the help of cyclooxygenase (COX) enzymes. There are two isoforms of COX. COX-1 is constitutively expressed and is present physiologically in all tissues, such as the gastrointestinal tract, blood vessels, platelets, and reproductive tissues. Hence, prostanoids play a role in various biological processes, including

platelet aggregation, vasoconstriction, pain perception, temperature regulation, the sleep-wake cycle, renal homeostasis, and gastrointestinal protection. COX-2 isoforms are inducible and are expressed at sites of inflammation. In general, NSAIDs inhibit the COX isoenzyme transiently and competitively, thereby inhibiting the biosynthesis of prostanoids. The therapeutic effects of NSAIDs are mainly due to COX-2 inhibition, and the adverse effects are primarily due to COX-1 inhibition. Although all the molecules act by inhibiting both isoforms, the extent of inhibition varies. The selectivity determines the extent of inhibition of anti-thrombotic and vasodilatory actions mediated through COX-2 versus pro-aggregatory and vasoconstrictive actions mediated through COX-1 and TXA-2 (Thromboxane A-2). The figure below illustrates the selectivity of COX-1 and COX-2 isoenzymes and the corresponding clinical implications for cardiovascular (CV) and gastrointestinal (GI) safety.




The COX-1: COX-2 selectivity of the commonly available NSAIDs and the corresponding impact on cardiovascular and gastrointestinal safety.

## Dosing and Administration

There are two major classes of NSAIDs: the conventional NSAIDs and the COX-2 inhibitors. The conventional NSAIDs are divided into various classes depending on their chemical properties. They are broadly classified into acidic and non-acidic compounds. The acidic compounds (e.g., diclofenac, ibuprofen) have a high affinity for protein binding and tend to accumulate and persist at sites of inflammation. The non-acidic compounds (e.g. celecoxib) are distributed homogenously throughout the body. Therefore, acidic NSAIDs such as diclofenac or ibuprofen are preferred for quick pain relief in inflammatory conditions, and they stay in inflamed joints (synovial fluid) even after serum drug levels decrease. The table below describes the various NSAIDs according to their chemical class, dosing, and half-lives.

***Properties of Commonly Used Non-Steroidal Anti-Inflammatory Drugs***

| Chemical Class & Drugs | Half-life (hours) | Dosing in mg/kg [maximum daily dose] & number of doses/day | Special Precautions/ Advice Toxicity/ Efficacy profile |
|---|---|---|---|
| Salicylic acid<br>• Aspirin | 4-6 | Anti-inflammatory dose: 80-100 mg/kg (< 25 kg); 2500 mg/m$^2$ (> 25 kg)<br>2-4 doses per day | Dose reduction by 50% in renal or liver failure. |
| Propionic acid<br>• Ibuprofen | 2 | 30-40 [2400]<br>3-4 doses per day | Risk of aseptic meningitis in lupus; most favourable (T/E) profile. |
| • Naproxen | 12-15 | 10-20 [1000]<br>2 doses per day | Cardiac safe, more GI toxicity; risk of pseudo-porphyria in children; Overall favourable (T/E) profile; naproxen sodium has a faster onset of action. |

| Chemical Class & Drugs | Half-life (hours) | Dosing in mg/kg [maximum daily dose] & number of doses/day | Special Precautions/ Advice Toxicity/ Efficacy profile |
|---|---|---|---|
| Acetic acid<br>• Diclofenac | 2 | 2-3 [200]<br>3 doses per day | Highest risk for transaminitis. Rapid onset of action and an ideal anti-inflammatory in arthritis.<br>Aceclofenac [100 mg twice daily] has better gastrointestinal tolerance, with other properties similar to those of diclofenac. |
| • Indomethacin | 2-13 | 1.5-3 [150]<br>3 doses per day | Higher risk for CNS side effects, GI intolerance, pedal oedema. More commonly used in conditions such as ankylosing spondylitis and gout. |
| • Etodolac | 6-7 | 10-20 [1000]<br>One dose per day | Once daily and extended-release formulations are useful. |
| Fenamic acids<br>• Mefenamic acid | | - [1000]<br>Three doses per day | Used for dysmenorrhea, higher GI side effects; lesser anti-inflammatory effects; not to be used for more than 3-7 days. |
| Oxicams<br>• Piroxicam | 3-86 | 0.2-0.3 [20]<br>One dose per day | Dose reduction in the elderly and liver impairment; least favourable T/E profile. |
| • Meloxicam | 20 | 0.25 [15]<br>One dose per day | Long duration, slow onset of action. |
| Non-acidic compounds<br>• Nabumetone | 24 | 30 [2000]<br>One dose per day | Tablets are mixed in water to create a slurry; caution is advised in older people and those with liver impairment. |

| Chemical Class & Drugs | Half-life (hours) | Dosing in mg/kg [maximum daily dose] & number of doses/day | Special Precautions/ Advice Toxicity/ Efficacy profile |
|---|---|---|---|
| COX-2 inhibitors | | | |
| • Celecoxib | 11 | - [200]<br>Two doses per day | Contraindicated in sulfa allergy. Preferred in patients with high CV and GI risk. |
| • Etoricoxib | 22 | - [120]<br>One dose per day | Ideal for young patients with Ankylosing spondylitis; increased risk for pedal oedema, hypertension. |
| • Polmacoxib | 131 | - [2]<br>One dose per day | Dual mode of action – inhibits carbonic anhydrase enzyme along with COX-2.<br>No major cardiovascular safety issue; indicated in primary osteoarthritis of knees and hips. |

*T/E: Toxicity/Efficacy profile; GI: gastrointestinal; CNS: central nervous system; COX: cyclooxygenase; CV: cardiovascular*

## Indications in Rheumatology

- In spondyloarthritis (axial), the role of NSAIDs in relieving inflammatory back pain cannot be overemphasised, as in the pre-biologic era, they used to be the drug of choice in patients with ankylosing spondylitis. Even now, as per the current recommendations, at least 2 NSAIDs need to be tried for 4 weeks before considering the option of biologics. The dramatic response of inflammatory back pain (IBP) to NSAIDs is a

criterion to confirm IBP. It also has evidence in preventing radiographic progression, considering its possible effect on bone healing.

- In rheumatoid arthritis, they may be used initially until the disease-modifying drugs start exerting their effect, or as rescue medication in flares.
- In gout, NSAIDs play a significant role in alleviating pain and inflammation during the acute gouty attack, either alone or in combination with colchicine or steroids. It can also be used in other crystal arthropathies.
- They can be used initially in systemic onset juvenile idiopathic arthritis or adult-onset Still's disease for the treatment of fever, arthritis, and serositis.
- NSAIDs have a role in managing the pain due to pleuritis or pericarditis in patients with lupus.
- In osteoarthritis, various soft tissue rheumatological disorders and regional pain syndromes, NSAIDs provide symptomatic relief, as well as in.
- Aspirin is used at high doses in the treatment of Kawasaki disease and acute rheumatic fever.

## Adverse Effects

- Gastrointestinal (GI) side effects are the most common adverse effects of NSAIDs. They are dyspepsia, esophagitis, gastroduodenal ulcers, their complications like bleeding, perforation and rarely colitis and small bowel erosions and strictures. GI side effects are more common with conventional NSAIDs, which have higher COX-1 activity. In patients with Spondyloarthritis and underlying inflammatory bowel disease,

one has to be careful with the usage of NSAIDs as they can exacerbate the underlying bowel inflammation.

- The common renal side effects are sodium retention, weight gain, oedema of the legs, and hypertension. The less common side effects include acute renal failure (in dehydrated patients), papillary necrosis (in people with diabetes), acute interstitial nephritis, acute exacerbation of chronic kidney disease and type 4 renal tubular acidosis with hyperkalaemia. In practice, pedal oedema and reduced urine output are seen more commonly with etoricoxib and indomethacin, though it can occur with any of the NSAIDs.
- Hepatic side effects are also seen rarely with NSAIDs, depending on the drug used. It is more common with diclofenac, aceclofenac and sulindac. Aspirin, particularly in children, is more notorious for causing Reye's syndrome. In clinical practice, aceclofenac or diclofenac, used alone or in combination with methotrexate, can cause transaminitis, particularly at higher doses and with long-acting preparations.
- Asthma can be exacerbated with aspirin or traditional NSAIDs. COX-2 inhibitors are preferred in patients with asthma or allergy. SAMTER's triad is aspirin-exacerbated airway disease, characterised by the triad of asthma, nasal polyposis and aspirin hypersensitivity. There can also be allergic reactions like cutaneous vasculitis, erythema multiforme, and Stevens-Johnson syndrome. Celecoxib (which has a sulfonamide group) needs to be avoided in patients with sulfa allergy. Pseudo-porphyria can be seen in children with juvenile idiopathic arthritis with the use of naproxen.

- Central nervous system side effects such as headache, dizziness, depression, hallucination or seizures are rarely seen with NSAIDs. The typical symptoms seen in adults are aseptic meningitis, psychosis and cognitive dysfunction. Aseptic meningitis is reported with ibuprofen and naproxen in patients with lupus and mixed connective tissue disease. Indomethacin and sulindac can cause psychotic symptoms.
- Hematologic issues such as aplastic anaemia, agranulocytosis and thrombocytopenia are rare side effects, and drugs causing these, like phenylbutazone, are no longer used due to these effects. It can also cause coagulation abnormalities, especially with aspirin.

## Drug Interactions

- With corticosteroids and selective serotonin reuptake inhibitors, NSAIDs increase the risk of gastrointestinal bleeding.
- They can increase the anticoagulant effect of warfarin.
- They reduce the antihypertensive effect of ACE inhibitors and Angiotensin receptor blockers. NSAIDs can reduce the antidiuretic effect of diuretics.
- Coadministration can reduce the efficacy of methotrexate.
- They increase the levels of drugs such as digoxin, lithium, phenytoin or valproate and increase the risk of their toxicity.
- NSAIDs, particularly ibuprofen and naproxen, can reduce the efficacy of aspirin by competing for the COX-1 isoenzyme.

## Clinical Challenges and Solutions

In practice, if the cardiovascular risk is higher with no GI risk, then naproxen is preferred. If both CV and GI risks are higher, a low-dose celecoxib is preferred. If both risks are low, any NSAID can be used. Whenever the GI risk is higher, proton pump inhibitors or misoprostol can be coadministered.

***Choice of NSAIDs Considering Cardiovascular, Gastrointestinal and Other Risks***

| Risk | Choice of non-steroidal anti-inflammatory drugs |
|---|---|
| Patient without CV risk | No GI risk factors: Any NSAID – intermittent and low dose<br>One or more GI risk factors: COX-2 selective inhibitor or conventional NSAID + PPI or misoprostol or H2 receptor antagonist<br>History of bleeding ulcer: COX-2 inhibitor + PPI or misoprostol |
| Patient with CV risk + one or more GI risk factors | CV risk <3%: Avoid COX-2 selective inhibitors, aceclofenac, diclofenac >100 mg/day and ibuprofen ⩾2400 mg/day<br>If concomitant administration of low-dose aspirin: Avoid traditional NSAIDs, particularly the ones with high affinity for COX-1 (ibuprofen and naproxen)<br>CV risk >3%: Administration of aspirin 2 hours before traditional NSAID (naproxen or ibuprofen) + PPI<br>Do not use NSAIDs within 3-6 months of an acute cardiovascular event. |
| Patient with CV risk + history of ulcer bleeding | If it is possible, avoid NSAIDs and COX-2 selective inhibitors<br>If strictly necessary and CV < 3%: (celecoxib or diclofenac <100 mg/day or ibuprofen<2400 mg/day or nimesulide) + PPI |

*NSAIDs: non-steroidal anti-inflammatory drugs; COX: cyclooxygenase; CV: cardiovascular; GI: gastrointestinal; PPI: proton pump inhibitors*

## Conclusion

To conclude, the choice of NSAID depends on efficacy, potential toxicity, the indication, patient-specific risk factors, the patient's preference, as well as the dosing schedule and the expected effect (anti-inflammatory vs. analgesic) in the given clinical situation. The two significant factors that determine the choice of NSAIDs are the CV and GI risk profile of an individual patient. It is always advisable to use NSAIDs for the shortest duration and intermittently, and it is better to avoid sustained-release, highly potent drugs.

### *Tips to Use NSAIDs Effectively*

- A risk assessment (mainly cardiovascular and gastrointestinal) should be done for each patient before selecting the appropriate NSAID.
- Choosing the right drug for the right patient minimises toxicity and enhances efficacy.
- Use the lowest effective dose for the shortest possible duration.
- If prescribed as an analgesic drug, stop administration after 7 days if no benefit is noted.
- If prescribed as an anti-inflammatory drug, stop administration after 3 weeks if no benefit is noted.
- If possible, avoid concomitant therapy with corticosteroids, anticoagulants, low-dose aspirin, or antiplatelet agents.

# METHOTREXATE

*Keerthi Talari Bommakanti*

Methotrexate (MTX) has been a mainstay molecule in rheumatology for decades, earning its place as the anchor drug in the management of many autoimmune rheumatic diseases. Even in the era of biologics and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), it remains unmatched in its combination of efficacy, affordability, and long-term data. However, much of its history has been shaped by misconceptions—many of which originate from the high-dose regimens used in oncology—which continue to influence its use today.

## Pharmacology

Every rheumatologist learns early on that MTX is a folic acid analogue that inhibits dihydrofolate reductase, thereby interfering with DNA synthesis and repair. But that's only the "textbook" part of the story. At the low doses used in rheumatology, MTX is less a cytotoxic weapon and more a subtle immune diplomat. Its real impact comes from boosting extracellular adenosine, a molecule with potent anti-inflammatory effects. Adenosine acts like a skilled negotiator, calming overactive immune responses, reducing pro-inflammatory cytokines, and modulating the behaviour of immune cells.

The range of conditions for which MTX is effective reads like a rheumatology handbook: rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus with arthritis or cutaneous predominance, vasculitis (including limited granulomatosis with polyangiitis and polyarteritis nodosa), myositis, systemic sclerosis with inflammatory arthritis, and enteropathic arthritis.

It works well as a solo performer—especially in early disease—but also plays effectively in combination, forming the backbone of DMARD therapy and pairing well with biologics. Its versatility is one reason it has weathered the competition from newer agents; few drugs can match MTX in both scope and cost-effectiveness.

## Dosing and Administration

If MTX had a "golden rule," it would be this: once a week, every week. Daily dosing can lead to severe toxicity and must be avoided. It is typically initiated at 10–15 mg weekly, with gradual increases to 25 mg/week or the highest tolerated dose to achieve disease control. Both oral and parenteral routes are effective; however, the subcutaneous route offers better bioavailability at higher doses and is often better tolerated in patients who experience gastrointestinal side effects.

Folic acid supplementation is essential, given as 1 mg daily (except on MTX day), folate reduces the risk of oral ulcers, gastrointestinal upset, and cytopenias without compromising the efficacy of MTX.

## Adverse Effects and Monitoring

Like any drug, MTX has its share of side effects. The common, nuisance-level ones—such as nausea, oral ulcers, fatigue, hair thinning, and mild elevations in liver enzymes—are familiar and usually manageable. The rare but more serious toxicities include hepatotoxicity, bone marrow suppression, and pulmonary toxicity.

Among the latter, MTX-induced hypersensitivity pneumonitis is rare (less than one per cent), presents acutely, and is entirely different from the chronic interstitial lung disease (ILD). This distinction is critical because one of the most persistent myths in rheumatology has been that MTX worsens RA-associated ILD. Multiple robust studies now show the opposite: low-dose MTX does not worsen ILD, and there is even evidence that it may prevent its development.

### *Monitoring*

Good monitoring keeps MTX safe. Before starting therapy, a complete blood count, liver function tests, renal function tests, and a baseline chest X-ray are essential. During treatment, blood counts and biochemistry should be checked every 2–4 weeks in the early phase, then every 8–12 weeks once the dose and test results are stable. Pulmonary function tests may be helpful if there is pre-existing lung disease or new respiratory symptoms.

## Contraindications

MTX should not be used in pregnancy and breastfeeding, in severe liver or renal impairment, active infections (including

tuberculosis), or significant alcohol use. Caution is advised in older people, in those with hepatic steatosis or viral hepatitis, and patients at risk for dosing errors.

## Challenges and Solutions

Barriers to optimal MTX use are often psychological and logistical. Some patients arrive fearful of the drug, often due to outdated information. Others are confused by the weekly dosing schedule, which can lead to errors. Clinicians may underdose or stop MTX prematurely, with side effects that may be manageable with slight changes in drug administration.

These issues can be addressed through repeated patient education, early use of the subcutaneous route in cases of intolerance, folic acid supplementation as a standard, and structured follow-up for monitoring. Even something as simple as linking the MTX dose to a fixed day—"Methotrexate Monday"—can prevent errors.

### *Myth-Busting*

MTX does not cause chronic lung or liver fibrosis at doses used in rheumatology. It does not worsen RA-associated ILD. The rare hypersensitivity pneumonitis it can cause is a separate, acute entity. Bone marrow suppression is rare and can be prevented with proper monitoring. The infection risk is modest and comparable to the disease background. The only consistent malignancy link is a slightly increased risk of non-melanoma skin cancer; no other associations have been found.

## History

MTX was first developed in the 1940s as a chemotherapeutic agent. In the 1980s, it was introduced into rheumatology practice for its immunomodulatory benefits at significantly lower doses. Within a decade, it was embedded in treatment guidelines worldwide. It has withstood scrutiny, remained cost-effective, and continues to be the first-line recommendation in most guidelines.

### *Why MTX Still Matters*

If MTX were launched today—with its proven efficacy, safety, and affordability—it would be hailed as a breakthrough. Instead, it is sometimes dismissed as "old." Yet the evidence is clear: MTX remains the most important DMARD in our arsenal, unmatched in its balance of benefits, risks, and cost.

## Conclusion

In a rapidly evolving therapeutic landscape, MTX remains a steady presence. It works across multiple diseases, combines well with other agents, and is safe with appropriate monitoring. Myths that once clouded its use are fading in the face of strong evidence. MTX is not just an old drug—it is a proven, adaptable, and essential ally in rheumatology practice.

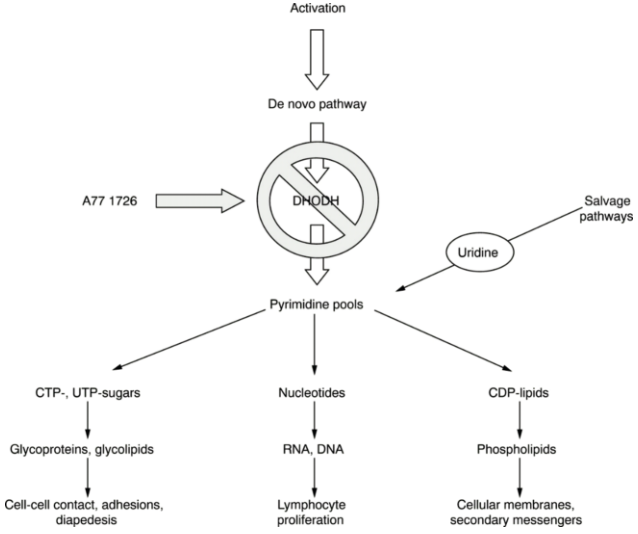
# LEFLUNOMIDE

*Gayatri Ekbote*

Leflunomide was approved by the US Food and Drug Administration (FDA) in 1998.

## Pharmacology

Leflunomide is an isoxazole-based immunomodulator. It arrests the growth of activated lymphocytes by inhibiting the enzyme dihydroorotate dehydrogenase, in turn inhibiting the production of uridine monophosphate. Leflunomide is rapidly metabolised to the active major metabolite A77 1726, which is responsible for the drug's pharmacologic activity.




*DHODH: dihydroorotate dehydrogenase; CTP: cytidine triphosphate; UTP: uridine triphosphate*

*Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2000;59:841-9.*

## Indications in Rheumatology

It is an FDA-approved, non-biological drug for the treatment of rheumatoid arthritis. It has both anti-inflammatory and immunomodulatory characteristics. It delays articular cartilage and bone disintegration, limiting irreversible joint damage. This medication reduces systemic inflammation.

Leflunomide is also indicated for the treatment of psoriatic arthritis; however, it is not yet an FDA-approved drug for psoriatic arthritis because it has minimal impact on skin disease.

Despite being a potent dihydro-orotate dehydrogenase inhibitor, it has not secured FDA approval for cancer treatment.

By inhibiting dihydro-orotate dehydrogenase, which arrests the S-phase in the cell cycle, it can slow the rapid proliferation of cancer cells; hence, its role in the treatment of malignancy requires exploration.

It can be used in combination with other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), most commonly with methotrexate. It can also be used in combination with biologic disease-modifying antirheumatic drugs (bDMARDs), such as rituximab. However, vigilance for toxicity is needed.

Leflunomide is used in juvenile inflammatory arthritis, systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis, dermatomyositis, and for treatment and remission maintenance in Wegener's granulomatosis (GPA). However, larger studies are needed to establish the use of leflunomide in these diseases.

## Dosing and Administration

Leflunomide is available in oral tablet form in doses of 10 mg and 20 mg. It can be administered as an oral loading dose of 100 mg once daily for three days, followed by a maintenance dose of 10 mg or 20 mg per day, depending on the patient's tolerance and response to treatment. However, the use of a loading dose is no longer encouraged due to an increased risk of toxicity and lack of evidence of additional efficacy. Leflunomide takes effect clinically in 4-8 weeks after initiation.

## Adverse Effects and Monitoring

- Gastrointestinal: Nausea, dyspepsia, diarrhoea, vomiting, abdominal pain and raised liver enzymes.
- Neurological: Headache, dizziness, parasthesia (however, these are uncommon).
- Cardiovascular: Hypertension can be seen, so blood pressure should be monitored.
- Respiratory: Interstitial lung disease has been reported.
- Haematological: Very rarely, pancytopenia.
- Cutaneous: Skin rash, alopecia (however, these are uncommon).

Hepatotoxicity is observed more commonly in patients receiving combination therapy with methotrexate and leflunomide. It is not recommended for those with preexisting liver disease.

Patients experiencing severe side effects of leflunomide should undergo a washout with cholestyramine or activated charcoal.

In animal studies, it has been proven to be teratogenic.

### *Monitoring*

Baseline tests, including a complete blood count (CBC), liver function tests (LFTs), and renal function tests, are recommended. Hepatitis B and C serology, HIV screen, and pregnancy test, if indicated, are recommended by the American College of Rheumatology (ACR) consensus guidelines at baseline. CBC and LFTs should be checked every 2–4 weeks for the first three months of treatment, and then every 8–12 weeks thereafter. More frequent monitoring is needed in case the dose is changed or if another DMARD is added.

## Contraindications and Precautions

It is contraindicated in pregnant women and breastfeeding mothers. It remains in the body for over 2 years and is thus usually avoided in women of childbearing age. A washout with cholestyramine, followed by checking the blood levels of the drug, is recommended in women on leflunomide who wish to conceive.

# SULFASALAZINE

*Akshat Pandey*

Sulfasalazine is a commonly prescribed anti-inflammatory and immunomodulatory drug with a sulfapyridine and 5-aminosalicylic acid (5-ASA / mesalamine or mesalazine) connected by an "azo" bond that provides unique pharmacological characteristics. Owing to its distinctive chemical composition and various mechanisms of action, sulfasalazine has emerged as a therapeutic option for addressing chronic inflammation and autoimmune diseases.

## Pharmacology

Intestinal bacteria metabolise sulfasalazine into sulfapyridine and 5-aminosalicylic acid (5-ASA). The active metabolite of sulfasalazine, sulfapyridine, primarily exerts systemic anti-inflammatory effects by suppressing the synthesis of inflammatory mediators, reducing leukocyte infiltration at inflammatory sites and modulating cytokine secretion. In contrast, 5-ASA offers localised protection to the intestinal mucosa, potentially through mechanisms such as scavenging oxidative free radicals, inhibiting neutrophil infiltration and preserving mucosal barrier integrity. The combined action of these components endows sulfasalazine with dual systemic and localised therapeutic efficacy.

## Indications in Rheumatology

Sulfasalazine is indicated for the treatment of chronic inflammatory diseases in rheumatology, such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, inflammatory

bowel disease (primarily for ulcerative colitis), and spondyloarthritis (including peripheral arthritis, uveitis, and may help alleviate stiffness in axial spondyloarthritis).

## Dosing and Administration

The usual dosage is 2-3 g daily, in two to three evenly divided doses. It is advisable to initiate therapy with a lower dosage of sulfasalazine, e.g., 0.5 to 1.0 g daily, to reduce possible gastrointestinal intolerance. A therapeutic response has been observed as early as 4 weeks after starting treatment with sulfasalazine, but therapy for 12 weeks may be required in some patients before clinical benefit is noted. Consideration can be given to increasing the daily dose of sulfasalazine to 3 g if the clinical response after 12 weeks is inadequate, though many people may not tolerate this dose. Careful monitoring is recommended for doses over 2 g per day.

## Adverse Effects and Monitoring

In recent years, despite the introduction of more effective therapies, such as biologics and targeted therapies like tofacitinib, sulfasalazine remains a cornerstone in clinical practice due to its cost-effectiveness and relative safety. Nevertheless, the adverse reactions linked to sulfasalazine should not be ignored. The primary source of these adverse reactions is its metabolite, sulfapyridine, which often results in toxic responses typical of sulfonamide medications, including headaches, nausea, vomiting, and various allergic reactions, usually appearing within the initial months of treatment. Overall, approximately 75% of adverse drug reactions (ADRs) occur within three months of initiating therapy and over 90% by six months. Some adverse effects are dose-dependent, and symptoms can frequently be mitigated by lowering the dosage.

The most frequently observed ADRs include nausea, headache, rash, loss of appetite, and elevated temperature, affecting about one-third of patients.

Hypersensitivity reactions include erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, Toxic Epidermal Necrolysis (TEN), epidermal necrolysis (Lyell's syndrome) with corneal damage, drug rash with eosinophilia and systemic symptoms (DRESS), anaphylaxis, serum sickness syndrome, among others. Many of the side effects, except for DRESS-like allergic reactions, are rare, though one should be aware of them.

Other serious adverse effects include blood dyscrasias, hepatitis, transverse myelitis and other neurological disorders, toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary tract infections, haematuria, crystalluria, proteinuria, and haemolytic-uremic syndrome.

Urine discolouration and skin discolouration are seen. The drug can cause reversible oligospermia. On stopping the medication, these effects reverse.

Sulfonamides share certain chemical similarities with some goitrogens, diuretics (such as acetazolamide and thiazides), and oral hypoglycaemic agents. Instances of goitre production, diuresis, and hypoglycaemia have occurred infrequently in patients receiving sulfonamides.

### *Monitoring*

Complete blood counts, including differential white blood cell counts and liver function tests, should be conducted before initiating sulfasalazine and biweekly during the first three months of treatment. In the subsequent three months, these tests should

be performed monthly and thereafter every three months or as warranted. Symptoms such as sore throat, fever, pallor, purpura, or jaundice may signal a severe blood disorder. If any of these symptoms arise, the patient should seek immediate medical attention.

## Precautions

- Sulfasalazine should be administered cautiously in patients with severe allergies or bronchial asthma.
- Sufficient fluid intake must be ensured to prevent crystalluria and stone formation.
- Patients with glucose-6-phosphate dehydrogenase deficiency should be closely monitored for signs of haemolytic anaemia, as this reaction is often dose-dependent.
- In patients with porphyria, sulfonamides must be avoided as they have been known to trigger an acute attack.
- If toxicity or hypersensitivity reactions occur, sulfasalazine should be stopped immediately. Patients should follow up with their healthcare providers to assess the need for ongoing treatment.

## Pregnancy and lactation

Sulfasalazine is safe during pregnancy and lactation. During pregnancy, folic acid supplementation is recommended, and caution is needed during lactation in low birth weight babies, as it can rarely cause bloody diarrhoea.

# HYDROXYCHLOROQUINE

*Madhuri HR*

Hydroxychloroquine (HCQ) is a derivative of quinine and a naturally occurring alkaloid. The first report of quinine's use in treating cutaneous lupus dates back to 1894. During the Second World War, when used as antimalarial prophylaxis, many soldiers reported improvement in skin rashes and joint pains, leading to further investigation for Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA).

Chloroquine is a synthetic derivative of quinine. With the addition of a hydroxyl group, HCQ was developed in 1955. This modification enhances bioavailability, prolongs the half-life, and exhibits a more favourable safety profile regarding ocular and cardiac toxicity.

## Pharmacology

HCQ is a weak base that can easily cross the cellular membranes. HCQ acts on multiple components of the immune system, although the precise mechanism is not yet elucidated. HCQ blocks Toll-like receptors 7 and 9 in Dendritic Cells, inhibits lysosomal function, and modulates antigen presentation by macrophages and dendritic cells. It also inhibits antibody production by B cells and decreases the activation of the complement pathway. It suppresses the auto-reactivation of T cells and reduces the production of pro-inflammatory cytokines, such as IFN-$\gamma$, TNF-$\alpha$, IL-1, and IL-2. HCQ also exerts an antithrombotic action by inhibiting platelet aggregation.

## Indications in Rheumatology

HCQ is recommended in the management of many rheumatological illnesses.

In RA, the benefit of HCQ in preventing joint damage is inferior to that of other disease-modifying antirheumatic drugs (DMARDs). It may be used only when there is low disease activity, without poor prognostic factors in treatment-naive patients, or as part of combination DMARD therapy when there is an inadequate response to Methotrexate.

HCQ is a central drug in the management of SLE. It has an established role in the management of SLE disease activity, cutaneous disease, renal manifestations, and pediatric SLE. HCQ improves mortality, reduces the risk of thrombotic events, has hypoglycemic and hypolipidemic effects, and decreases cardiovascular events in patients with SLE. The use of HCQ in the pre-conceptional period and during pregnancy in SLE has been shown to improve the maternal and fetal outcomes, control disease activity, and decrease the risk of flares during pregnancy and in the post-partum period.

In Antiphospholipid Antibody Syndrome (APS), numerous in vitro and in vivo studies have demonstrated the efficacy of HCQ in mitigating endothelial dysfunction and the procoagulant effects of anti-phospholipid antibodies (aPL). A decrease in the titres of the antibodies has been demonstrated. As there is no increased risk of bleeding, HCQ forms an essential adjunct to anticoagulation in the treatment of APS. In obstetric APS, the addition of HCQ improves placental dysfunction, reduces complement activation, and decreases the incidence of

pregnancy-related complications. Although commonly administered, the evidence for the role of HCQ in primary thrombosis prevention in subjects with high-risk aPL profiles with or without non-thrombotic clinical manifestations is weak.

In Sjögren's syndrome, HCQ can be used to manage fatigue, musculoskeletal pain, and cutaneous involvement. The efficacy of HCQ in managing sicca symptoms is a matter of controversy. The risk of congenital heart block in the offspring of mothers with Anti-Ro/SSA positivity is decreased by HCQ.

Due to the excellent safety profile, the off-label use of HCQ in many other diseases, including Sarcoidosis, Dermatomyositis, and Osteoarthritis, is common. The efficacy of HCQ in preventing the progression of preclinical RA and incomplete SLE needs better evidence.

***ACR and EULAR recommendations on the use of hydroxychloroquine in various diseases***

| Disease | Guidelines | Recommendation | Comments |
|---|---|---|---|
| Rheumatoid Arthritis | ACR 2021 guidelines and the EULAR 2022 Update on management of RA | Initiation of treatment in DMARD-naive patients with low disease activity, HCQ is conditionally recommended over other csDMARDs.<br>HCQ is also used as part of "Triple Therapy," which refers to a combination of HCQ, sulfasalazine, and either methotrexate or leflunomide. | HCQ is better tolerated and has a more favourable risk profile in patients with RA.<br>Triple therapy may be preferred in lower-resource settings as well as in patients with specific comorbidities for whom triple therapy may be associated with significantly less risk of adverse events. |

| Disease | Guidelines | Recommendation | Comments |
|---|---|---|---|
| SLE | The 2025 ACR Guidelines for the Treatment of SLE | In people with SLE, routine treatment with HCQ is strongly recommended unless contraindicated. | |
| SLE | The EULAR recommendations for the management of systemic lupus erythematosus: 2023 update | HCQ is recommended for all patients, unless contraindicated, at a target dose of 5 mg/kg actual body weight/day. | The dose may be individualised based on risk for flare and retinal toxicity. |
| Class III/IV or Class V Lupus Nephritis | The 2024 ACR Guidelines for the Screening, Treatment, and Management of Lupus Nephritis (LN) | In people with LN who are not already on HCQ, the initiation and continuation of HCQ to manage and prevent extra-renal manifestations is strongly recommended. | HCQ reduces the risk of mortality in people with SLE, including those with lupus nephritis. Dose adjustment for low GFR should be considered because kidney disease is a risk factor for retinal toxicity. |
| APS | The 2019 EULAR recommendations for the management of antiphospholipid syndrome in adults | In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing the heparin dose to a therapeutic dose or the addition of HCQ or low-dose prednisolone in the first trimester may be considered. | The role of HCQ in preventing primary thrombosis in APS requires further research. |

| Disease | Guidelines | Recommendation | Comments |
|---|---|---|---|
| Pregnancy in SLE/APS | The 2017 EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy, and menopause in patients with SLE/APS | HCQ is recommended preconceptionally and throughout pregnancy in those with SLE; it may also be used to manage flares during pregnancy. | |
| Pregnancy in SLE/APS | The 2020 ACR Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases | All women with SLE should take HCQ during pregnancy, unless there is a contraindication. | |
| Sjögren's syndrome | The 2020 EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies | In patients with frequent episodes of acute musculoskeletal pain, the use of HCQ has been proposed. It is also recommended in the management of cutaneous manifestations. | |
| Pregnancy in mothers with anti-Ro/SSA antibodies | The 2017 EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with SLE/APS | HCQ may reduce the odds of conduction defects in foetuses exposed to maternal anti-Ro/SSA antibodies, especially in mothers who have already had a child with Complete Heart Block. | |

*ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; DMARD: disease-modifying anti-rheumatic drugs; cs: conventional synthetic; HCQ: hydroxychloroquine; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; APS: antiphospholipid antibody syndrome*

## Adverse Effects and Monitoring

The recommended dose of HCQ is 5mg/kg body weight per day. It is administered orally and is rapidly absorbed with a bioavailability of 80%. The drug is metabolised by dealkylation in the liver, via the cytochrome P450 pathway, and excreted by the kidneys, with a half-life of approximately 40 days.

Although well-tolerated, some adverse events may occur, including gastrointestinal intolerance, abdominal pain, and diarrhoea.

***Cutaneous reactions:*** Drug rashes, pruritus, and hyperpigmentation are the most common cutaneous adverse events with HCQ. Rare instances of Stevens-Johnson's syndrome or Toxic Epidermolysis Necrolysis have been reported.

Long-term usage of HCQ may lead to cumulative toxicity in the form of cardiac and retinal toxicity.

***Retinal Toxicity :*** The risk factors for retinal toxicity include daily dose, duration of exposure, renal failure, and the presence of concomitant ocular disease or the use of ocular toxic drugs, such as Tamoxifen. The primary site of damage is the photoreceptor layer, followed by the retinal pigment epithelium (RPE). The classically described bull's-eye maculopathy represents an advanced stage of HCQ retinopathy caused by a parafoveal ring of RPE degeneration sparing a foveal island. There are many patterns and classifications of HCQ retinopathy, including parafoveal and pericentral distributions. Visual acuity is not compromised until the advanced stage of HCQ toxicity, when

symptoms may include blurring of vision, loss of peripheral vision, and impaired night vision. The American Academy of Ophthalmology recommends a baseline fundus examination, followed by annual screening after 5 years of use. The recommended screening tests include automated visual fields and spectral-domain optical coherence tomography (SD-OCT). Although HCQ retinal toxicity is not reversible, the goal of screening is to prevent vision loss by early recognition. If detected, the decision to stop the drug should be shared by the patient, the ophthalmologist, and the clinician, depending on the individual situation.

***Cardiotoxicity*** **:** Prolonged use of HCQ may lead to cardiac conduction defects or nonspecific adverse cardiac events, like ventricular hypertrophy, hypokinesia, heart failure, pulmonary hypertension, and valve dysfunction. In case of serious conduction blocks, the drug needs to be withdrawn.

Other rare adverse events include neurotoxicity, including vertigo, headache, and tinnitus. Myotoxicity may present with myalgias and proximal myopathy with elevated creatinine kinase levels.

### *Monitoring*

Studies have shown a positive correlation between HCQ levels in the blood and control of disease activity in SLE. Genetic polymorphisms in the CYP3A5*3, CYP3A4*18B, and CYP2D6*10 enzymes may contribute to variations in blood levels of these enzymes. There is considerable debate on the therapeutic and

target levels of HCQ concentration. Levels below 500 ng/mL suggest poor compliance and an increased risk of disease flares, while values beyond 1000 ng/mL are associated with decreased disease activity. The association between blood levels and retinopathy is unclear.

The 2023 Update of the EULAR recommendations for the management of SLE suggested the use of monitoring HCQ blood levels to guide the optimal dose for each patient and assess for possible non-adherence to therapy. Wherever feasible, levels may be used to titrate the dosage of HCQ.

# RITUXIMAB

*Kavitha MM*

Rituximab's history and development are landmark achievements in cancer immunotherapy. Ronald Levy and colleagues at IDEC Pharmaceuticals developed it. It became the first monoclonal antibody approved by the US Food and Drug Administration (FDA) for cancer therapeutics in 1997 for the treatment of relapsed or refractory follicular B-cell lymphoma. The indications expanded to the treatment of autoimmune diseases. Rituximab has revolutionised the treatment of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) and rheumatoid arthritis (RA). It has replaced cyclophosphamide as the drug of choice in life-threatening AAV and has been an effective add-on in rheumatoid arthritis when conventional treatment regimens fail. Although no large trials favour its use in systemic lupus erythematosus (SLE), it has been an effective treatment in SLE, particularly in India, where belimumab and anifrolumab have not yet been introduced.

## Pharmacology

Its mechanism of action is multifaceted, involving not only direct B-cell depletion but also broader immune modulation. Rituximab is a chimeric monoclonal antibody targeting CD20. CD20 is a surface protein that is expressed on B cells from the pre-B to mature B-cell transition. Once Rituximab binds to CD20, it results in B-cell depletion through antibody-dependent cellular cytotoxicity, apoptosis, and complement activation.

This results in rapid and profound depletion of B cells, but the anatomical compartment plays a significant role in its efficacy. Circulating B cells in peripheral blood achieve near-total depletion, but the results are less consistent when it comes to resident B cells in secondary lymphoid organs, such as the spleen or lymph nodes. CD20 is not expressed in plasma cells, which are the primary antibody-secreting cells. This explains why rituximab is sometimes less effective in achieving sustained improvement in patients.

Rituximab exerts its effect on T cell functioning by disrupting B cell-mediated antigen presentation. It reduces the number of activated T cells and enhances the Treg population, thereby reducing inflammation. Rituximab exerts its action in both RA and SLE by effectively breaking the B-cell-T-cell auto-reactive loop.

## Indications in Rheumatology

- Rheumatoid Arthritis
  - Uncontrolled diseases on conventional synthetic disease-modifying anti-rheumatic drugs
  - Interstitial lung disease
  - Vasculitis – Mononeuritis multiplex, skin ulcers
  - Organ-threatening complications: Scleromalacia, scleritis
- AAV
  - Life-threatening/organ-threatening – upfront
- Inflammatory Myositis
  - With interstitial lung disease
  - Resistant to conventional treatment

- SLE
  - Resistant cytopenia, Lupus nephritis
- IgG4RD
  - Multifocal organ-threatening manifestations of IgG4-related diseases respond well to rituximab and reduce the dose of steroids used.
- Systemic sclerosis: In progressive interstitial lung disease associated with systemic sclerosis not responding to mycophenolate mofetil, rituximab has been used. Its B-cell depletion effect can modulate fibrosis and inflammation.
- Steroid-dependent/ resistant Immune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA)
- Mixed connective tissue disease and Sjögren's disease: With interstitial lung disease and neurological involvement, such as mononeuritis multiplex, not responding to conventional treatment, rituximab can be used
- In demyelination associated with autoimmune disorders

Though off-label indications of rituximab are extensive, its usage is often limited due to a lack of robust data in diseases other than RA and AAV.

## Dosing and Administration

Rituximab is administered as two intravenous infusions of 1000 mg each, 14 days apart, in patients with rheumatoid arthritis. Follow-up doses are given after 6 months, depending on the clinical response. Lower doses have also been used with success in a specific subset of patients. This dosage schedule is also followed for other indications, except in vasculitis, where it is

administered as 500 mg every week for 4 weeks. The chances of infusion-related hypersensitivity reactions are high with rituximab; hence, it should be started at 50mg/hour, slowly increased, and always be preceded by pre-medication with methyl prednisolone. The usual re-treatment interval is 6 months (24 weeks), but if the situation warrants, it can be reduced to 16 weeks, provided it is never less than that. Re-treatment at 6 months is highly individualised in rheumatoid arthritis and usually on-demand rather than fixed dosing.

A fixed 6-month interval dosage is warranted for remission maintenance in AAV. The dosage can be either 500 mg or 1000 mg, based on the patient's profile, and should be administered for at least 2 years. In severe cases or patients with frequent relapses, maintenance dosage can be extended up to 5 years.

## Adverse Effects and Monitoring

Infusion-related hypersensitivity reactions, increased susceptibility to infections, reactivation of HBV and prolonged hypogammaglobulinemia are some common side effects. Rare but life-threatening side effects include progressive multifocal leukoencephalopathy.

### *Work-up Before Initiating Rituximab*

Hepatitis B and C: Rituximab is strongly associated with hepatitis B virus reactivation, which can be severe and life-threatening in some cases. This can happen in patients who are chronic HBV carriers (HBsAg Positive) and individuals with resolved infection (HBsAg Negative and anti-HBc positive). Reactivation can lead to acute hepatitis, liver cell failure and increased mortality. All patients planned on rituximab therapy

should undergo HBsAg and anti-HBc antibody testing. If positive and if rituximab therapy is mandatory, such patients should be initiated on anti-viral therapy before starting rituximab. Regular monitoring of HBV DNA is needed during and after rituximab therapy, and the antiviral prophylaxis should be continued at least 18 months after cessation of rituximab therapy to avoid late reactivation.

Whether Rituximab reactivates HCV infection is highly debatable, although we routinely screen for it before initiating treatment. Rituximab can be administered with close monitoring in patients with HCV positivity without cirrhosis under expert guidance. This information is extrapolated from oncology-based guidelines, where rituximab is the treatment of choice for many B-cell lymphomas.

Tuberculosis: Screening for latent tuberculosis infection (LTBI) is recommended; however, the risk of TB reactivation with rituximab is lower compared to anti-TNF agents. Clinical examination and chest X-ray to rule out active tuberculosis are mandatory. Although Mantoux or IGRA (Interferon Gamma Release Assay) is preferred to rule out LTBI, there are no clear guidelines on treatment and follow-up regarding this concerning rituximab, as the chances of reactivation are low. The decisions are individualised.

Immunoglobulin and CD 20 levels: The occurrence of hypogammaglobulinemia and infections is the most dreaded side effect of rituximab for a rheumatologist. This raises a question: Do we need to check CD20 levels/ immunoglobulin levels before starting rituximab? In a resource-limited setting, is it scientifically warranted? Indian guidelines and expert

recommendations emphasise checking baseline immunoglobulin levels before initiating rituximab to assess the risk of infection. This aligns with international consensus on rituximab use. They advise obtaining routine total serum Immunoglobulin levels (total Ig or IgG) before rituximab administration. However, longitudinal testing before each dosage depends on institutional protocols and is less defined. This is more commonly followed in dermatology practice regarding pemphigus, particularly when the chances of infection are high. No guidelines recommend routine CD20 testing before and after rituximab.

## Vaccinations and Rituximab

Rituximab impairs the immune response to new antigens; hence, vaccines are ideally given 4 weeks before rituximab. After receiving rituximab, it's best to wait at least 6 months before vaccination. In rabid dog bites, patients require immunoglobulin treatment, regardless of the wound category. Cell culture vaccines are administered, and rabies-neutralising antibody testing is performed 2 weeks after the last dose to assess the immune response.

## Conclusion

Rituximab has earned its place as a game changer in rheumatology for specific autoimmune diseases, provided that careful patient selection and risk mitigation strategies are applied, making it a 'drug worth it' in modern rheumatology care.

# TUMOUR NECROSIS FACTOR INHIBITORS

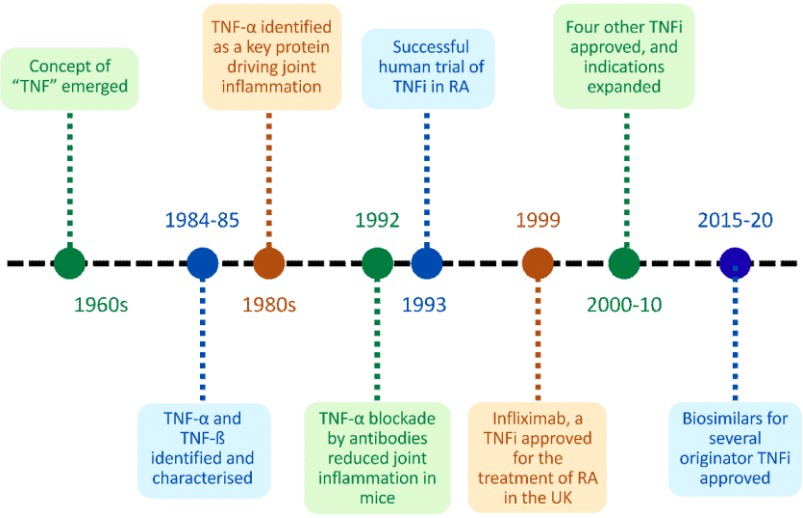
*Himanshu Pathak*

Tumour necrosis factor-alpha (TNF-α) is a pivotal pro-inflammatory cytokine primarily synthesised by activated macrophages, monocytes, and T cells. It plays a crucial role in inflammatory cascades, which are central to various autoimmune and inflammatory conditions. While essential for host defence at lower concentrations, excessive TNF-α production drives chronic inflammation and tissue damage.

TNF inhibitors (TNFi) are a class of biologic agents that have reshaped the therapeutic landscape for inflammatory arthritis and other autoimmune diseases by specifically targeting and neutralising TNF-α. Unlike conventional disease-modifying antirheumatic drugs (DMARDs), these biologics are engineered to target specific molecular pathways implicated in disease pathogenesis precisely.

Five FDA-approved TNFi are currently available: etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab. These agents exhibit distinct molecular structures and origins, contributing to their unique pharmacokinetic and immunogenic profiles.

The journey of TNFi spans several decades, showcasing the power of translational research.




***The history and evolution of Tumour Necrosis Factor inhibitors***

*TNF: tumour necrosis factor; TNFi: tumour necrosis factor inhibitor; RA: rheumatoid arthritis*

## Pharmacology

TNF-α is synthesised as a precursor protein and undergoes proteolytic cleavage to yield soluble TNF, which then oligomerizes into a biologically active homotrimer. Both soluble and transmembrane forms of TNF-α interact with two distinct TNF receptors: TNFRI (p55) and TNFRII (p75).

TNFi neutralise the pro-inflammatory actions of TNF-α by preventing its interaction with cellular TNF receptors. Monoclonal antibodies directly bind to both soluble and transmembrane forms of TNF-α, while etanercept acts as a 'decoy receptor,' binding to both TNF-α and TNF-β.

## Indications in Rheumatology

TNFi play a crucial role in managing various chronic inflammatory conditions in rheumatology, particularly for patients who have not achieved an adequate response to conventional disease-modifying antirheumatic drugs (DMARDs).

***Indications of Tumour Necrosis Factor Inhibitors in Rheumatology***

| Approved indications | Off-label indications |
|---|---|
| Rheumatoid Arthritis<br>Ankylosing Spondylitis<br>Psoriasis and Psoriatic Arthritis<br>Inflammatory Bowel Disease<br>Juvenile Idiopathic Arthritis<br>Hidradenitis Suppurativa<br>Noninfectious Uveitis | Behcet's Disease<br>Sarcoidosis<br>Pyoderma Gangrenosum<br>Granulomatosis with Polyangiitis<br>Systemic Lupus Erythematosus<br>Inflammatory Myopathy<br>Takayasu Arteritis<br>Polyarteritis Nodosa<br>Relapsing Polychondritis |

Their ability to significantly decrease inflammatory markers and prevent radiologic damage indicates their profound impact on altering the disease course, not merely managing symptoms.

***Overview of Key Tumour Necrosis Factor Inhibitors***

| Drug Name | Molecular Type | Route of Administration |
|---|---|---|
| Infliximab | Chimeric mA | IV |
| Adalimumab | Human mAb | SC |
| Etanercept | Receptor Fusion Protein | SC |
| Golimumab | Human mAb | SC or IV |
| Certolizumab Pegol | PEGylated Fab fragment | SC |

*mAb: monoclonal antibody; IV: intravenous; SC: subcutaneous*

## Dosing and Administration

TNF inhibitors are administered parenterally, either as a subcutaneous (SC) injection or intravenous (IV) infusion. Some TNFi may have a more frequent or higher "induction dose", followed by the "maintenance" dose.

Patient adherence is critical for treatment success. The choice between subcutaneous and intravenous administration has a significant impact on patient adherence, influenced by factors such as convenience, travel burden, and the integration of lifestyle.

## Side Effects and Monitoring

While TNFi have revolutionised treatment, their use is associated with a spectrum of adverse effects, ranging from common and minor to severe and potentially fatal. The FDA has issued 'boxed warnings' for TNF inhibitors due to the potential for serious adverse events. Common side effects include injection site reactions, infusion reactions, and systemic effects such as headache, nausea, and cough.

### Serious side effects

- Infections: The most significant risk encompasses bacterial, fungal, viral, and atypical infections.
- Tuberculosis Reactivation: A significant concern, particularly within the initial months of treatment.
- Malignancies: A small but elevated risk of developing certain cancers has been observed.
- Cardiovascular Effects: TNFi can exacerbate heart failure.

- Demyelinating Disorders: Rarely associated with the onset or exacerbation of central nervous system demyelinating diseases.
- Autoimmune Syndromes: Paradoxical development of autoimmune conditions has been reported.

Common side effects include injection site reactions, infusion reactions, and systemic effects such as headache, nausea, and cough.

Rigorous monitoring is crucial for mitigating risks associated with TNF inhibitor therapy. This includes pre-treatment screening for infections, vaccinations, physical examination, and baseline laboratory tests. Ongoing monitoring during treatment involves infection management, cardiac monitoring, neurological monitoring, haematological monitoring, and therapeutic drug monitoring.

## Contraindications and Precautions

Absolute contraindications include active serious infections, New York Heart Association (NYHA) Class III or IV Heart Failure, history of demyelinating disease, and administration of live vaccines.

Precautions and special considerations include screening for latent infections, hepatitis B and C status, concomitant use of other immunosuppressants, older age and comorbidities, surgery, and haematological parameters.

## Challenges in Clinical Use and Solutions

### *Clinical challenges*

- Primary Non-Response (PNR): Occurs when patients fail to achieve a clinical response within a defined period, and occurs in approximately 10-40% of patients.
- Secondary Loss of Response (LOR): Occurs in up to 50% of patients over time, with an annual rate ranging from 5-20%.
- Immunogenicity and Anti-Drug Antibody (ADA) Formation: The patient's immune system recognises the biological drug as foreign, leading to the production of ADAs.
- Patient Compliance and Adherence: Complex regimens and inconsistencies in provider interactions can significantly limit patient adherence.
- High Cost and Inconvenience: TNF inhibitors are expensive and may require clinic visits for administration.

### *Solutions and Optimisation Strategies*

- Therapeutic Drug Monitoring (TDM): Measuring drug serum concentrations and ADA/NAb levels to guide treatment optimisation.
- Immunomodulator Co-therapy: Co-administration with conventional DMARDs to reduce ADA formation and improve drug survival.
- Optimising Dosing Regimen: Proper dose adjustment and considering switching and re-switching TNFi therapy.
- Patient Education: Encouraging continuous adherence and maintaining a regular treatment dosing schedule.

- Biosimilars: Increasing availability has significantly reduced treatment costs and improved access.

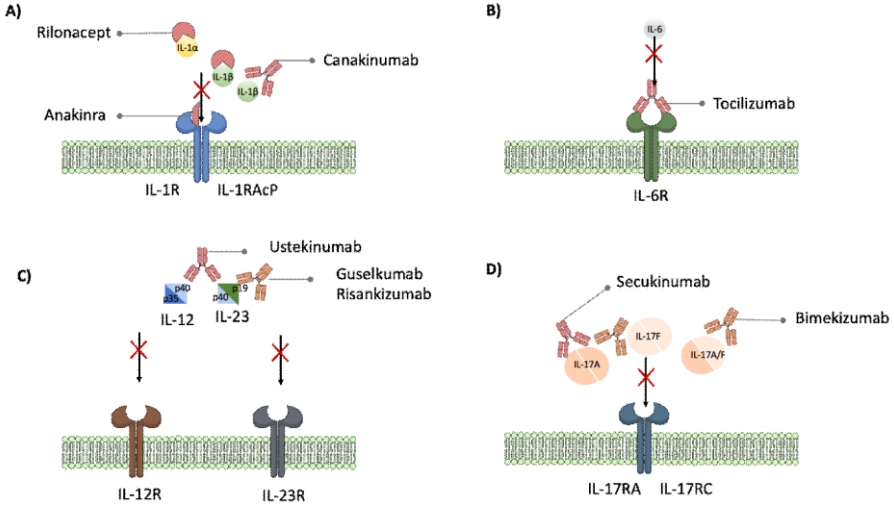
## Conclusion

TNFi have dramatically enhanced the quality of life for millions of patients with chronic inflammatory diseases. Their effective and safe utilisation demands a comprehensive approach to patient care, including rigorous pre-treatment screening, vigilant ongoing monitoring, and meticulous management of contraindications and precautions. Challenges such as primary non-response, secondary loss of response, and immunogenicity are increasingly addressed through personalised strategies. The historical trajectory of TNF inhibitors underscores the dynamic nature of medical science and reflects a continuous pursuit of more effective, safer, and accessible treatments for chronic inflammatory conditions.

# INTERLEUKIN INHIBITORS

*Pankti Mehta*

The therapeutic landscape in rheumatology has expanded significantly with the introduction of interleukin (IL) inhibitors targeting key inflammatory pathways. Currently available agents include inhibitors of IL-1 (anakinra, canakinumab, rilonacept), IL-6 (tocilizumab, sarilumab), the IL-12/23 axis (ustekinumab), IL-23 (guselkumab, risankizumab, tildrakizumab), and the IL-17 family (secukinumab, ixekizumab, brodalumab, bimekizumab). While additional IL inhibitors such as dupilumab and mepolizumab have shown promise in other immune-mediated diseases, this article will focus on agents commonly used in rheumatology practice, with an emphasis on those currently available in India.




***Mechanism of drugs targeting the IL (Interleukin)-1 (A), IL-6 (B), IL-12/23 (C), and IL-17 (D) pathways***

IL: Interleukin

## IL-1 INHIBITORS

Anakinra and Canakinumab are the available IL-1 inhibitors.

### Pharmacology

- Anakinra is a recombinant IL-1 receptor antagonist that binds to IL-1R1, acting as a competitive antagonist
- Canakinumab is a monoclonal antibody that binds IL-1β, preventing its interaction with the receptor
- Rilonacept is an IL-1R1 fusion protein that binds to both IL-1 and IL-1β

### Indications in Rheumatology

Systemic juvenile idiopathic arthritis (sJIA), Adult-onset Still's disease (AOSD), Gout, Cryopyrin-associated periodic syndromes

### Dosing and Administration

- Anakinra: 100 mg subcutaneously (SC) daily
- Canakinumab: 150 mg SC every 4-8 weeks, single dose for gout flares

### Adverse Effects and Monitoring

#### *Common Adverse Effects*

Injection site reactions, headache, upper respiratory infections.

#### *Serious Adverse Effects*

Neutropenia (especially when co-administered with tumour necrosis factor inhibitors), infections including tuberculosis (TB) and reactivation of viral hepatitis

### *Monitoring*

Complete blood count (CBC), liver and renal function

## Contraindications and Precautions

- Active infections
- Dose modification in renal impairment for anakinra
- Avoid live vaccines
- Limited data on safety in pregnancy

## Challenges

Daily injections with anakinra may affect adherence.

## Trivia

- Anakinra was one of the first biologics targeting a specific cytokine receptor, but lost popularity due to daily dosing
- Its short half-life (4–6 hours) makes anakinra especially useful in critically ill patients, where rapid withdrawal is sometimes necessary
- A cardiovascular trial (CANTOS) showed that canakinumab reduced cardiovascular events by targeting inflammation

## IL-6 INHIBITORS

Tocilizumab and Sarilumab are the available IL-6 inhibitors

## Mechanism of Action

Both are monoclonal antibodies targeting the IL-6 receptor, blocking downstream pro-inflammatory signalling.

## Indications in Rheumatology

Rheumatoid arthritis (RA), sJIA, AOSD, Systemic Sclerosis, Giant cell arteritis (GCA), Takayasu arteritis, Cytokine release syndromes

## *Dosing and Administration*

- Tocilizumab: Intravenous (IV) 4-8 mg/kg monthly for RA, 6 mg/kg monthly for GCA, 8-12 mg/kg 2 weekly for sJIA. SC 162 mg every 2 weeks
- Sarilumab: 200 mg SC every 2 weeks.

## Adverse Effects

### *Common Adverse Effects*

Injection site reactions, upper respiratory infections, headache, elevated liver enzymes, dyslipidemia.

### *Serious Adverse Effects*

Gastrointestinal perforation, neutropenia

### *Monitoring*

CBC, liver function, lipid panel

## Contraindications and Precautions

- Diverticulitis (risk of GI perforation)
- Elevated transaminases
- Limited data for use in pregnancy
- Avoid live vaccines

## Challenges

GI side effects are under-recognised.

## Trivia

- Tocilizumab was initially developed for Castleman's disease
- CRP monitoring is of limited value when on tocilizumab
- Associated with "lipid paradox"

# IL-12/23 INHIBITOR

Ustekinumab is an IL-12/23 inhibitor

## Pharmacology

Targets the p40 subunit shared by IL-12 and IL-23, inhibiting both pathways involved in Th1 and Th17 responses.

## Indications in Rheumatology

Psoriatic arthritis (PsA), Psoriasis, Inflammatory bowel disease (IBD)

## Dosing and Administration

Weight-based dosing, 45 mg (<100 kg) or 90 mg (≥100 kg) SC at week 0, 4, then every 12 weeks

## Adverse Effects

### *Common Adverse Effects*

URTIs, headache, fatigue.

### *Serious Adverse Effects*

Infections

## Contraindications and Precautions

- Hypersensitivity to Ustekinumab
- Avoid live vaccines
- Limited data for use in pregnancy

## Trivia

Ustekinumab was the first biologic to target both IL-12 and IL-23.

## IL-17 INHIBITORS

Secukinumab, Ixekizumab, Bimekizumab and Brodalumab are IL-17 inhibitors.

## Pharmacology

- Secukinumab and ixekizumab target IL-17A
- Brodalumab targets the IL-17 receptor A (associated with suicide risk in trials)
- Bimekizumab (blocks both IL-17A and IL-17F).

## Indications in Rheumatology

PsA, axial spondyloarthritis, and psoriasis.

## Dosing and Administration

- Secukinumab: 150–300 mg SC at weeks 0, 1, 2, 3, 4, then monthly
- Ixekizumab: 160 mg loading dose, then 80 mg SC every 4 weeks
- Bimekizumab: 320 mg every 4 weeks for the first 16 weeks, followed by 160 mg every 4 weeks

## Adverse Effects

### *Common Adverse Effects*

Candidiasis, nasopharyngitis, diarrhoea.

### *Serious Adverse Effects*

IBD exacerbation, infections, suicidal tendency (only for brodalumab, black boxed)

## Contraindications and Precautions

- Active IBD
- Active infection
- Limited data for use in pregnancy
- Avoid live vaccines

## Trivia

- IL-17 blockade is uniquely associated with mucocutaneous candidiasis due to its role in mucosal immunity.
- Highly effective for psoriasis, peripheral joints and axial involvement in PsA.

# IL-23 INHIBITORS

Guselkumab, Risankizumab and Tildrakizumab IL-23 inhibitors

## Pharmacology

Monoclonal antibodies targeting the p19 subunit of IL-23, blocking Th17 differentiation.

## Indications in Rheumatology

PsA and psoriasis

## Dosing and Administration

- Guselkumab: 100 mg SC at week 0, 4, then every 8 weeks
- Risankizumab: 150 mg SC at week 0, 4, then every 12 weeks

## Adverse Effects

### *Common Adverse Effects*

URTIs, headache

### *Serious Adverse Effects*

Infections

## Contraindications and Precautions

- Active infections
- Limited data for safety in pregnancy

## Trivia

- Emerging data on the prevention of progression from psoriasis to PsA.
- Highly effective for psoriasis, peripheral joints, and IBD, with emerging evidence for axial involvement in PsA.

## Conclusion

Interleukin inhibitors offer targeted therapy for a range of inflammatory diseases. In India, tocilizumab and secukinumab are widely available, while the availability of the others remains limited. With the increasing development of biosimilars, access and affordability are expected to improve. Judicious selection based on disease domain, patient comorbidities, and cost can optimise outcomes while minimising risks.

# JANUS KINASE INHIBITORS

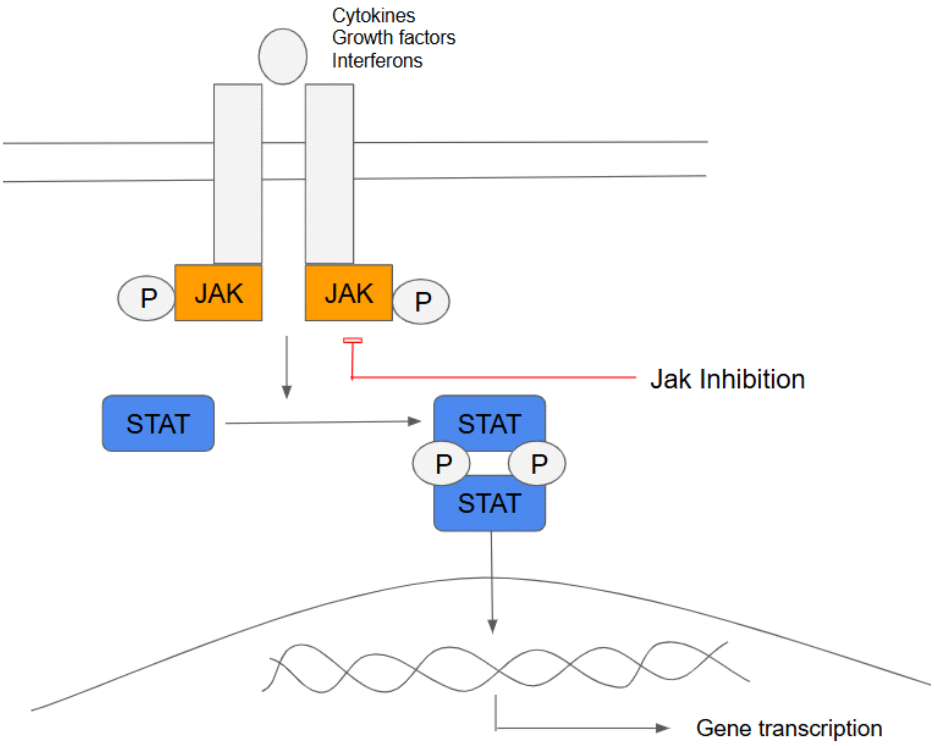
*Vikramraj K Jain*

Janus kinase (JAK) inhibitors (JAKi) are a new class of targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) that interfere with the signal transduction pathways of various cytokines, thereby mediating immune-modulatory benefits across a broad range of disease processes. They have evolved as effective treatment options for autoimmune rheumatic diseases and are rewriting the treatment landscape.

## Pharmacology

JAKs belong to the tyrosine kinase family that binds to cytokines and growth factors, resulting in their phosphorylation, which in turn activates and recruits transcription factors of the signal transducer and activator of transcription proteins (STAT) family. These activated proteins translocate to the nucleus, where they induce transcription. There are four JAK isoforms (JAK1, JAK2, JAK3 and TYK2).

Cytokines (Interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6 and IL-12), interferons, endocrine factors and colony-stimulating factors act through JAKs. Their inhibitors interfere with the ATP-binding site of JAKs, resulting in the suppression of downstream signalling pathways.




### *Mechanism of Action of JAK Inhibitors*

*JAK: Janus kinase; STAT: signal transducer and activator of transcription proteins*

JAK inhibitors are a new class of oral therapies targeting multiple pathways of the immune system. Those effective in rheumatological conditions include tofacitinib, barcitinib, upadacitinib and filgotinib.

## Indications in Rheumatology

JAK inhibitors are approved for the treatment of several autoimmune diseases.

***Different Janus Kinase Inhibitors and their approved indications***

| Molecule | Approved Indications in Rheumatology |
|---|---|
| Tofacitinib | Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Juvenile Idiopathic Arthritis (JIA) |
| Baricitinib | Rheumatoid Arthritis |
| Upadacitinib | Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Non-radiographic axial Spondyloarthritis |
| Filgotinib | Rheumatoid Arthritis |

JAKi are considered in most autoimmune conditions in patients who have failed conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or biologic disease-modifying antirheumatic drugs (bDMARDs). Currently, there is no direct evidence of the superiority of one JAK inhibitor over another.

### *JAK Inhibitors in Common Rheumatological Conditions*

*Rheumatoid arthritis:* JAKi are used for the treatment of adult patients with moderate to highly active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.

*Psoriatic arthritis:* Used for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.

*Ankylosing spondylitis:* Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

## Dosing and Administration

JAK inhibitors are typically administered orally, once or twice daily.

***Usual Doses of Available JAK Inhibitors***

| Drug | Usual Dose (Adults) |
|---|---|
| Tofacitinib | 5 mg twice a day or 11 mg extended release once a day |
| Baricitinib | 2–4 mg once a day |
| Upadacitinib | 15 mg once a day |
| Filgotinib | 200 mg once a day |

With severe hepatic disease (Child-Pugh C), JAKi should not be used. In severe renal disease (Creatinine Clearance (CrCl) <30 mL/min), a reduction in dosage is recommended for tofacitinib to 5 mg once daily; however, baricitinib is not recommended if CrCl is < 30 mL/min. With CrCl 30–60 mL/min, baricitinib should be used at 2 mg daily. No dosage reduction is currently recommended for other JAKi.

### *Drug interactions (Tofacitinib)*

- Strong CP3A4 inhibitors (e.g., ketoconazole) cause increased exposure to tofacitinib; hence, its dose should be reduced.
- Moderate CYP3A4 inhibitors coadministered with strong CYP2C19 Inhibitors (e.g., fluconazole) cause increased exposure to tofacitinib; hence, its dose should be reduced.
- Strong CYP3A4 inducers (e.g., rifampin) - cause decreased exposure to tofacitinib and may result in loss of or reduced clinical response, hence consider an increase in dosage.

- Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine) increase the risk of added immunosuppression, while coadministration with biologic DMARDs or potent immunosuppressants has not been studied.

## Adverse Effects and Monitoring

### *Common Adverse Effects*

- Upper respiratory tract infections
- Headache
- Nausea, diarrhoea
- Elevated lipids (HDL, LDL)
- Transaminase elevation
- Elevations of CPK are noted with JAK inhibitors but have not been associated with clinical events
- Elevations of creatinine have been noted with JAK inhibitors, but have not been associated with renal failure or hypertension
- Acne lesions

### *Potentially Serious Adverse Effects*

- Serious infections (similar to bDMARDs), opportunistic infections including TB, Herpes zoster (increased rates compared to bDMARDs)
- Rates of malignancy do not appear elevated with JAK inhibition, although the risk of non-melanoma skin cancer (NMSC) may be elevated.
- Lymphopenia, thrombocytopenia, neutropenia, anaemia may occur

- An increased risk of venous thromboembolism (VTE) has been reported in a safety trial of RA among patients using 10 mg twice a day tofacitinib and within the placebo-controlled trial period of baricitinib in patients with RA.

### *Monitoring*

- Full and differential blood counts and liver transaminase tests at 1 and 3 months and then periodically, such as every 3 months; lipid levels at 3 months.
- Annual skin examination (for detection of skin cancer).

## Contraindications and Precautions

- Severe active (or chronic) infections, including TB and opportunistic infections
- Current malignancies
- Severe organ dysfunction, such as severe hepatic disease (Child-Pugh C) or severe renal disease
- Pregnancy and lactation
- Recurrent VTE (unless anticoagulated)
- Gastrointestinal Perforations: To be used with caution in patients who may be at increased risk
- Avoid live vaccines while on JAK inhibitors
- As there is a higher incidence of infections in the elderly population in general, caution should be used when treating older patients (>65 yrs)
- Do not initiate tofacitinib if absolute lymphocyte count <500 cells/mm3, an absolute neutrophil count (ANC) <1000 cells/mm3 or haemoglobin <9 g/dL

## Challenges in Clinical Use and Solutions

***Common challenges with JAK inhibitors and how to overcome them***

| Challenge | Solutions |
|---|---|
| Risk of Herpes Zoster | Consider prior recombinant zoster vaccination in high-risk patients. |
| Thromboembolic risk | Avoid in patients with known venous thromboembolism (VTE) or high cardiovascular (CV) risk. |
| Drug interactions (e.g., CYP3A4) | Review concomitant medications before starting. Rifampicin may cause inadequate response to tofacitinib; hence, one can use only isoniazid for latent tuberculosis treatment with tofacitinib or increase the dosage of tofacitinib. |
| Perioperative period for orthopaedic surgery | Withhold medication (tofacitinib) for 3 days before surgery. |
| Planning to conceive | Stop at least 4 weeks before trying to conceive. |

## History and Trivia

The name is derived from the two-faced Roman god of beginnings, endings, and duality, Janus, because the JAKs possess two nearly identical phosphate-transferring domains. One domain exhibits the kinase activity, while the other regulates the kinase activity of the first.

## Conclusion

The advent of JAK inhibitors has been a great addition to the armamentarium of rheumatologists. The spectrum of their use has been expanding rapidly. However, their use is not without risks and needs special precautions and monitoring.

# AZATHIOPRINE AND CALCINEURIN INHIBITORS

*Parthajit Das*

## AZATHIOPRINE

Despite the emergence of biological treatment and immunotherapies, Azathioprine (AZA), a well-established immunosuppressive drug, still plays a pivotal role in the management of various rheumatological conditions. We will explore its clinical applications, dosage considerations, and strategies for managing its potential adverse effects to optimise therapeutic outcomes.

## Pharmacology

Azathioprine, the 1-methyl-4-nitroimidazol-5-yl derivative of mercaptopurine, is a prodrug and converted to its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN), under the influence of hypoxanthine-guanine phosphoribosyltransferase (HPRT) and thiopurine methyltransferase (TPMT) enzymes. Its metabolites are incorporated into the replicating DNA and inhibit purine synthesis. 6-MP is primarily inactivated in the liver by xanthine oxidase (XO), whereas in extra-hepatic tissues, 6-MP undergoes inactivation by thiopurine-S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) enzymes. Patients with reduced TPMT or NUDT15 activity may have excessive cellular concentrations of active 6-thioguanine nucleotides (6-TGNs) and an increased risk of severe myelosuppression. After oral administration, intact AZA is undetectable in the blood due to extensive first-pass metabolism. AZA is absorbed rapidly through the GI system and does not penetrate the blood-brain barrier. It is excreted via the kidneys, thereby increasing its toxicity in renal failure.

## Indications in Rheumatology

Azathioprine (AZA) was approved by the Food and Drug Administration (FDA) for the symptomatic treatment of active rheumatoid arthritis. However, it is no longer routinely used for arthritis, but rather for extra-articular manifestations, such as interstitial lung disease.

AZA has been used off-label for the treatment of the following rheumatic conditions:

- Systemic lupus erythematosus
- ANCA-associated vasculitis, IgA vasculitis
- Behcet disease
- Inflammatory myositis
- Non-infectious uveitis
- Relapsing polychondritis
- Pyoderma gangrenosum
- Interstitial lung disease
- Others – Azathioprine has been successfully used as a maintenance therapy for the management of relapsing polychondritis and IgG4-related diseases.

## Dosing and Administration

- Recommended dosage: It may be started at 1 mg/kg/day and slowly titrated up to a maximum dose of 2-2.5 mg/kg/day.
- Treatment initiation: A Specialist Rheumatology team should initiate AZA therapy at 25 mg once a day and escalate by 25 mg every week until a maintenance dose is reached (usually up to 100-200 mg daily). The maximum daily dose is 250 mg.
- Treatment maintenance: Usual dose is 100-200 mg daily (in divided doses). Some patients may respond to lower doses of the medication.

- Caution: Lower dose is advised in case of significant renal or hepatic impairment, in the older population, in patients with mild to moderate impaired bone marrow function, TPMT deficiency or NUDT15 mutation.
- Time to response: Approximately 6-8 weeks. Treatment withdrawal or additional therapy may be considered if no improvement occurs within 3 months.

## Adverse Effects and Monitoring

### *Common Adverse Effects*

- Nausea, vomiting, anaemia.
- Leukopenia and/or thrombocytopenia are dose-dependent and may occur late in the course of therapy. Dose reduction or temporary withdrawal may result in reversal of cytopenias.
- Less common side effects are skin rashes, alopecia, fever, arthralgias, and Sweet's Syndrome (acute febrile neutrophilic dermatosis).

### *Potentially Serious Adverse Effects*

Patients with absent or very low thiopurine methyltransferase (TPMT) activity pose a risk of life-threatening pancytopenia.

Patients receiving AZA are at higher risk for bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections. These infections may have a fatal outcome.

## Contraindications and Precautions

- Hypersensitivity to 6-mercaptopurine (6-MP) or ingredients should alert the prescriber to probable hypersensitivity to AZA.
- Systemic sepsis or known malignancy.

## Challenges in Clinical Use and Solutions

- Pregnancy and lactation: AZA is compatible with pregnancy and lactation.
- In older people: Strict monitoring is advised, especially with impaired renal function, moderately impaired hepatic function and mild or moderately impaired bone marrow function.
- Drug interactions: Allopurinol interferes with the metabolism of azathioprine, thereby increasing plasma levels of 6-MP, resulting in potentially fatal blood dyscrasias. Therefore, a 50-75% dose reduction of azathioprine is advised
- Patients with TPMT or NUDT15 activity are at increased risk of myelosuppression. Substantial dose reduction is generally required.

## CALCINEURIN INHIBITORS

Calcineurin inhibitors (CNIs) are a class of immunosuppressants that includes cyclosporine, Tacrolimus, Pimecrolimus, and Voclosporin.

## Pharmacology

Immunophillins, including cyclophillins and FK-binding proteins, are a family of cytoplasmic proteins present in most cells. Cyclosporin binds with cyclophillins, whereas Tacrolimus and pimecrolimus bind with FK-binding proteins. This drug-receptor complex competitively binds to and inhibits calcineurin, a calcium- and calmodulin-dependent phosphatase. Subsequently, this leads to the inhibition of the translocation process of a family of transcription factors (NF-AT), resulting in reduced transcriptional activation of cytokine genes for interleukin (IL)-2, tumour necrosis factor (TNF)-α, IL-3, IL-4, CD40L,

granulocyte-macrophage colony-stimulating factor, and interferon-gamma. Ultimately, the proliferation of T lymphocytes is reduced. Voclosporin inhibits calcineurin, p-glycoprotein, and organic anion-transporting polypeptides 1B1 and 1B3, contributing to its potential as a promising immunosuppressant. CNIs undergo significant first-pass metabolism, resulting in a reduced bioavailability for both cyclosporine and tacrolimus. Cytochrome P450 system enzymes, primarily CYP3A4 and CYP3A5, are the major contributors to the metabolism of CNIs.

## Indications in Rheumatology

- Rheumatoid arthritis
- Psoriasis
- Lupus nephritis
- Inflammatory myositis
- Interstitial lung disease

## Dosing and Administration

***Cyclosporin:*** Available oral preparations are 10 mg, 25 mg, 50 mg, and 100 mg. An oral solution (50 mg/mL) and ophthalmic emulsions are available in concentrations of 0.05% and 0.1%.

***Tacrolimus:*** Available oral formulations are 0.5 mg, 1 mg, and 5 mg. The topical formulation is accessible as an ointment with concentrations of 0.03% or 0.1%.

***Pimecrolimus:*** Topical pimecrolimus is available in a 1% concentration cream.

***Voclosporin:*** The recommended dosage is 23.7 mg, twice daily, along with mycophenolate mofetil and corticosteroids.

## Adverse Effects and Monitoring

### *Cyclosporin and Tacrolimus*

- Hypertension
- Neurotoxicity - tremors, headaches, seizures, and, in rare cases, encephalopathy
- Metabolic abnormalities - hyperlipidaemia, hyperkalaemia, hyperuricemia, gout, hypomagnesemia, and glucose intolerance.
- Both cyclosporine and tacrolimus have the potential to induce hepatotoxicity.
- Immunosuppressive effect - life-threatening bacterial, viral, and fungal infections.
- Malignancies such as squamous cell cancers and lymphoproliferative disorders may be associated with CNIs.
- Long-term therapy has potential for nephrotoxicity, hence creatinine must be monitored.

### *Pimecrolimus*

- Application site: Erythema, irritation, burning and stinging.
- Headache, fever, influenza-like conditions, infections, and respiratory symptoms such as sinusitis, tonsillitis,

### *Voclosporin*

- Hypertension, headache, dizziness, migraine, seizure, alopecia, hypertrichosis, acute kidney injury, anaemia, tremors, gastrointestinal tract disturbances.

## Contraindications and Precautions

- Hypersensitivity reactions to the drug or polyoxyethylated castor oil.
- Cyclosporine should be avoided in patients with psoriasis who are simultaneously undergoing PUVA or UVB therapy.

## Challenges in Clinical Use and Solutions

***Hepatic impairment:*** Cyclosporine, Tacrolimus, Voclosporin - dose reduction is necessary in cases of mild-to-moderate hepatic impairment, while its use is contraindicated in patients with severe hepatic impairment.

***Renal impairment:*** Cyclosporine, Tacrolimus, Voclosporin - renal impairment warrants cautious monitoring because of the potential risk of nephrotoxicity. The use of voclosporin is not recommended in patients with a baseline estimated GFR ≤45 mL/min/1.73 m2.

***Pregnancy and breastfeeding considerations:*** The 2020 guidelines from the American College of Rheumatology conditionally recommend using cyclosporine and tacrolimus during pregnancy and breastfeeding. Pimecrolimus should be applied immediately after nursing, following thorough cleansing of the nipples before lactation. Voclosporin should be avoided during breastfeeding and for at least 1 week following the final dose of the medication (as per the manufacturer's recommendation).

# MYCOPHENOLATE MOFETIL AND CYCLOPHOSPHAMIDE

*Sunitha Kayidhi*

## MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF), a fermentation product of Penicillium species, was first described by Gosio in 1896 as an antimicrobial agent against anthrax. Later, in 1989, it was shown to prolong the survival of the graft in an experimental heterotopic heart transplantation model. The first human study was conducted in patients with severe refractory rheumatoid arthritis.

### Pharmacology

- MMF is a reversible, competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), which catalyses a rate-limiting step in the de novo synthesis of purine nucleotides. IMPDH has an inducible isoform (Type II) upregulated only in proliferating T and B lymphocytes. Mycophenolic acid (MPA) is a pharmacologically active metabolite of MMF, which inhibits this isoform 5 times more than the type I isoform present in resting lymphocytes.
- MPA inhibits adhesion molecule glycosylation and expression, as well as lymphocyte and monocyte recruitment.
- MPA also exerts its anti-proteinuric effects beyond immunosuppression by directly influencing podocyte structure and architecture.
- MMF acts by reducing TGF-β expression and thus decreases the proliferation of pulmonary fibroblasts in patients with idiopathic pulmonary fibrosis

- Mycophenolic acid is 80 to 97% albumin-bound, converted to a glucuronide by glucuronyl transferase, and is primarily (90%) excreted in the urine.
- Half-life of the drug is 16 hrs, and the metabolism is hepatic.

## Indications in Rheumatology

***List of Indications in Rheumatology***

| |
|---|
| Systemic Lupus Erythematosus (SLE)<br>Induction (Single/combination) and maintenance therapy for class III, IV and V lupus nephritis Non-renal SLE |
| Idiopathic inflammatory myositis |
| Anti-synthetase syndrome |
| Connective Tissue Disease-associated Interstitial Lung Disease |
| ANCA-associated vasculitis |
| Takayasu arteritis |
| Urticarial vasculitis |
| Behcet's disease |
| IgA nephropathy |
| Inflammatory bowel disease |
| Inflammatory eye disease |
| Pyoderma gangrenosum |
| Autoimmune haemolytic anaemia |
| Idiopathic thrombocytopenic purpura |
| Autoimmune hepatitis |
| Sarcoidosis |
| Panniculitis |
| Pemphigus/pemphigoid |
| IgG4-related disease |

## Dosing and Administration

- The drug is to be taken orally, ideally on an empty stomach. Capsules or tablets of mycophenolate mofetil 250 mg and 500 mg, and sulfate salts in 360 mg, 500 mg and S-720 mg strengths, and a 200mg/mL oral suspension are used in rheumatology.
- It is started at a dose of 500 mg daily, and increased by 500 mg weekly until the optimum (2 g) or maximum tolerated dose (3 g) is reached.
- The mean absolute bioavailability after oral administration is 94%. Taking the medication with food does not reduce absorption, but it does decrease the maximal concentration in the plasma by 20-40%.
- Enteric-coated mycophenolate sodium (EC-MPS) reduces the GI side effects, primarily by delaying the release of MPA into the small intestine rather than the stomach.
- No dose adjustments required for mild and moderate renal impairment. Dose should not exceed 1g twice daily in severe renal impairment (GFR <25 mL/min). Dialysis does not eliminate MMF.
- MMF dose does not require adjustment in liver failure (but it is to be noted that low albumin can increase the levels of MMF).

## Adverse Effects and Monitoring

### *Common adverse effects*

- Diarrhoea, nausea, vomiting and abdominal pain
- Infections

### *Uncommon adverse effects*

- Leukopenia, lymphopenia
- Skin rash
- Elevated liver enzymes
- Headaches, dizziness, difficulty sleeping and tremors

### *Monitoring*

Blood counts and liver enzymes should be done monthly initially, then every 1-3 months once the patient is on a stable dose of the medication.

## Contraindications and Precautions

- Pregnancy (MMF should be stopped at least 6 weeks before conception)
- Lactation
- Hypersensitivity to mycophenolate
- Active infection

Live vaccinations should be avoided, and contraception should be practised while using MMF.

## Challenges in Clinical Use and Solutions

- Gastrointestinal intolerance can be overcome in many patients by using the sulfate salt of the drug.
- A proton pump inhibitor (PPI) can help reduce gastric intolerance, but a sufficient time gap must be given between the PPI and MMF, as PPIs can reduce the absorption of MMF.
- MMF is expensive and is not widely available in many places (mainly rural). Advocacy is required for the inclusion of

rheumatological diseases and such expensive but essential medicines in government schemes and insurance coverage.

- Compliance with therapy and monitoring can be improved by patient education and counselling.

## CYCLOPHOSPHAMIDE

Cyclophosphamide (CYC) is derived from the warfare gas Nitrogen mustard. Goodman and Gilman recognised CYC's potential to suppress white blood cells and reduce lymph nodes, resulting in its introduction into cancer treatment.

### Pharmacology

- CYC belongs to the class of alkylating agents that substitute alkyl radicals into DNA with nucleophilic bases, thus inhibiting key functions such as DNA replication and transcription, resulting in cell death.
- CYC exerts its immunosuppressive action by decreasing the numbers of T and B lymphocytes, decreasing lymphocyte proliferation, decreasing antibody production, and suppressing delayed hypersensitivity to new antigens.
- CYC is an inactive prodrug that is rapidly absorbed and oxidised to 4-hydroxy cyclophosphamide, which later decomposes by hepatic microsomal enzymes into phosphoramide mustard, an active metabolite and acrolein, which is responsible for the toxic side effects of the drug.
- Half-life is 4-10 h in adults and 1-6.5 hours in children. Metabolism is hepatic, and excretion is primarily renal (>75%).

## Indications in Rheumatology

***List of Indications in Rheumatology***

| |
|---|
| Systemic Lupus Erythematosus (SLE) |
| Class III and IV lupus nephritis |
| Neuropsychiatric SLE and other severe organ involvement |
| ANCA-associated vasculiti |
| Renal, Diffuse alveolar haemorrhage and severe systemic disease |
| Systemic Polyarteritis Nodosa |
| Behcet's disease |
| Takayasu arteritis |
| Inflammatory myositis and Overlap myositis |
| Progressive skin disease in Systemic Sclerosis |
| Connective Tissue Disease-associated Interstitial Lung Disease |
| Sjögrens Disease |
| Rheumatoid vasculitis |
| Catastrophic Antiphospholipid Syndrome |
| Cryoglobulinemic vasculitis |
| Sarcoidosis |
| Cardiac and Central Nervous |
| Relapsing polychondritis |
| IgG4-related disease |
| Refractory inflammatory eye disease |

## Dosing and Administration

It is available in oral and intravenous (IV) formulations.

### *Vasculitis*

2 mg/kg PO daily OR 15mg/kg IV every two weeks for three doses and then every 3 weeks.

### *Lupus Nephritis*

***Euro–lupus protocol*:** 500 mg IV every 2 weeks for 6 doses.

***National Institute of Health Protocol*:** 500-750mg/m2 of body surface area monthly for 6 months, followed by optional maintenance doses every 3 months until 1 year after remission.

### *Oral Dose*

1.0–1.5 mg/kg/d (maximum 150 mg/d) for 2–6 months.

***Cyclophosphamide dosing as per renal function***

| Creatinine clearance (ml/min) | Intravenous dose | Oral dose (mg/kg) |
|---|---|---|
| >50 | Standard dosing as per indication | |
| 25-50 | Decrease dose by 30% | 1.2 |
| 15-25 | | 1 |
| <15 | | 0.8 |
| On dialysis | Give the drug 12-24 hours after dialysis. | |

### *Hepatic Dose Adjustments*

The half-life of CYC may be increased from the regular eight hours to 12 hours in cases of liver failure, but it is not hepatotoxic, so dose adjustments are not required.

## Adverse Effects and Monitoring

### *Common Adverse Effects*

- Nausea/vomiting, diarrhoea, anorexia
- Alopecia, skin pigmentation changes, rash, nail damage
- Leukopenia, neutropenia
- Infections
- Amenorrhea

### *Serious Adverse Effects (Mostly dose-dependent)*

- Ovarian failure (age-dependent)
- Azoospermia
- Haemorrhagic cystitis
- The concurrent use of sodium-2-mercaptoethane sulfonate (mesna) may detoxify acrolein, CYC's bladder-toxic metabolite, and thus reduce bladder toxicity.
- Two-to-four fold increased risk of bladder, skin, myeloproliferative and oropharyngeal cancers (mainly with oral cumulative doses of >80g of CYC).

### *Rare side effects*

- Pneumonitis and pulmonary fibrosis
- Cardiotoxicity

### *Monitoring*

- Haemogram initially once in 2 weeks, then once monthly and once monthly urine examination.
- Avoid giving CYC if Platelets <50 000/mm3 and/or if white blood cell count <3500/mm3 (absolute neutrophil count <1500 cells/µL).

## Contraindications and Precautions

### *Contraindications*

- Pregnancy (absolute contraindication in the first trimester; however, it can be given in the second and third trimesters in life-threatening or organ-threatening situations).
- Lactation
- Hypersensitivity to the drug
- Active infection
- Urinary tract outflow obstruction

### *Precautions*

- Ensure adequate Hydration
- Antibiotic prophylaxis against Pneumocystis infection
- Avoid live vaccines
- Pregnancy should be planned only after three completed months after taking CYC to avoid teratogenicity.

## Challenges in Clinical Use and Solutions

- Intravenous dosing regimens can reduce the cumulative dose burden as opposed to daily oral dosing.
- It is challenging to administer CYC in a resource-limited setting because it requires supervision while infusing the drug and monitoring for side effects. This can be addressed by coordinated care with a multidisciplinary team of rheumatologists, primary care physicians, and nurses. Patient education and the use of digital health tools make monitoring easier.

# APREMILAST, IGURATIMOD AND COLCHICINE

*Upendra Rathore*

## APREMILAST

### Pharmacology

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4). PDE4 is an enzyme that degrades cyclic adenosine monophosphate (cAMP). Inhibition leads to an increase in intracellular cAMP, which in turn modulates inflammatory responses. Apremilast reduces the expression of pro-inflammatory cytokines, such as Tumour Necrosis Factor (TNF)-$\alpha$, Interleukin (IL)-23, and Interferon (IFN)-$\gamma$, while increasing the expression of anti-inflammatory cytokines, like IL-10.

### Indications in Rheumatology

- Psoriatic Arthritis (PsA) – US Food and Drug Administration (FDA) approved
- Oral ulcers in Behçet's disease – FDA approved
- Off-label: Cutaneous lupus, ankylosing spondylitis, and dermatomyositis (emerging evidence)

### Dosing and Administration

- Initiation involves a slow uptitration over 6 days to minimise gastrointestinal (GI) symptoms, till a dose of 30 mg twice daily is reached, which is then continued.
- Renal impairment: Adjust dose to 30 mg once daily if Creatinine Clearance (CrCl) <30 mL/min.

## Adverse Effects and Monitoring

### *Common Adverse Effects*

- Nausea, diarrhoea, headache
- Weight loss
- Upper respiratory tract infections

### *Serious Adverse Effects*

- Depression or suicidal ideation (rare but reported)
- Severe weight loss

### *Monitoring*

- No lab monitoring required routinely
- Periodic weight checks and mental health assessments

## Contraindications and Precautions

- Avoid in patients with a history of depression unless the benefits outweigh the risks.
- Use with caution in underweight patients.

## Challenges in Clinical Use and Solutions

- It has high dropout rates due to GI intolerance. Careful titration and patient education can increase acceptance and adherence.
- It has modest efficacy compared to biologics, so it is best suited for patients with mild disease or in combination with conventional synthetic disease-modifying antirheumatic drugs.

### Trivia

Apremilast was developed following the success of PDE inhibitors in dermatology and was approved by the FDA for PsA in 2014. Its oral formulation and immunomodulatory mechanism have made it an attractive alternative to biologics in resource-limited settings.

## IGURATIMOD

### Pharmacology

Iguratimod (IGU) is a novel oral synthetic disease-modifying antirheumatic drug (DMARD) with both anti-inflammatory and immunomodulatory effects. It inhibits nuclear factor-kappa B (NF-κB) and suppresses the production of cytokines (IL-1, IL-6, TNF-α) and immunoglobulins by B cells. It also inhibits osteoclast differentiation, providing bone-protective effects.

### Indications in Rheumatology

- Approved for Rheumatoid Arthritis (RA).
- Used as an add-on therapy in patients with inadequate response to methotrexate (MTX).
- Off-label indications include spondyloarthritis, lupus, and interstitial lung disease (ILD)-related arthritis.

### Dosing and Administration

- Usual dose: 25 mg twice daily orally.
- May be combined with MTX or other DMARDs.

## Adverse Effects and Monitoring

### *Common Adverse Effects*

- Nausea, gastritis
- Elevated liver enzymes
- Dizziness

### *Serious Adverse Effects*

- Hepatotoxicity
- Leukopenia and thrombocytopenia
- Interstitial pneumonitis (rare but serious)

### *Monitoring*

- Haemogram and liver function tests at baseline and every 2–4 weeks initially, then every 2-3 months.
- Chest imaging if the drug is used in interstitial lung disease-prone patients.

## Contraindications and Precautions

- Contraindicated in pregnancy (teratogenic).
- Avoid in patients with pre-existing liver disease or significant pulmonary fibrosis.

## Challenges in Clinical Use and Solutions

- Limited global approval restricts its usage outside Asia. Consider in select patients with refractory RA in countries where it is approved.
- It has overlap toxicity with MTX. Regular monitoring and dose adjustment are required.

### Trivia

Iguratimod was first approved in Japan in 2012 and later in China. Unlike most DMARDs, it is derived from a non-steroidal anti-inflammatory drug (NSAID) scaffold and represents a bridge between NSAIDs and traditional immunosuppressants.

## COLCHICINE

### Pharmacology

Colchicine is a plant alkaloid extracted from Colchicum autumnale. It binds to tubulin, preventing microtubule polymerisation. This disrupts neutrophil chemotaxis, phagocytosis, and degranulation. It also inhibits inflammasome activation and IL-1β production.

### Indications in Rheumatology

- Gout – acute attack and prophylaxis
- Familial Mediterranean Fever (FMF)
- Pericarditis – recurrent or post-pericardiotomy
- Off-label: Scleroderma-related pericarditis, Behçet's disease, osteoarthritis (experimental)

### Dosing and Administration

- Acute gout attack: 1.2 mg initially, followed by 0.6 mg 1 hour later.
- Prophylaxis: 0.6 mg once or twice daily.
- FMF: 1.2–2.4 mg/day

It is commonly available as a 0.5 mg tablet.

Dose adjustment is necessary in cases of renal or hepatic impairment, as well as in the elderly.

## Adverse Effects and Monitoring

### *Common Adverse Effects*

- Diarrhoea, nausea, abdominal cramps
- Fatigue, hair loss (with long-term use)

### *Serious Adverse Effects*

- Myopathy, especially with statins
- Bone marrow suppression
- Rhabdomyolysis
- Toxicity in renal failure

### *Monitoring*

- Haemogram, renal and liver function tests periodically
- Creatine kinase levels if muscle symptoms occur

## Contraindications and Precautions

- Severe renal or hepatic impairment
- Concurrent use of CYP3A4 inhibitors (e.g., clarithromycin) increases the risk of toxicity
- Caution in the elderly and malnourished

## Challenges in Clinical Use and Solutions

- GI intolerance limits compliance, so start with lower doses and titrate upward slowly.
- It has interactions with various commonly used medications, thus requiring vigilant review of the medication list before prescription.

## Trivia

Colchicine has one of the oldest histories in medicine, mentioned in ancient Egyptian texts. It was FDA-approved for gout only in 2009, despite centuries of use. It recently gained attention for its potential use in COVID-19 due to its anti-inflammatory properties.

***Key Points to Know About Apremilast, Iguratimod and Colchicine***

| Parameter | Apremilast | Iguratimod | Colchicine |
|---|---|---|---|
| Mechanism of Action | PDE4 inhibitor → ↑cAMP → ↓TNF-α, IL-17, IL-23, ↑IL-10 | NF-κB inhibition → ↓pro-inflammatory cytokines, inhibits B cells, osteoclasts | Microtubule polymerization inhibitor → ↓neutrophil chemotaxis, ↓IL-1β |
| Primary Use in Rheumatology | Psoriatic arthritis, Behçet's ulcers | Rheumatoid arthritis (add-on to MTX) | Gout (acute and prophylaxis), FMF, pericarditis |
| Off-label Uses | Cutaneous lupus, dermatomyositis | Spondyloarthritis, CTD-ILD-related arthritis | Behçet's disease, scleroderma pericarditis, osteoarthritis (experimental) |
| Common Side Effects | Nausea, diarrhoea, headache, weight loss | Nausea, liver enzyme elevation, gastritis | Diarrhoea, nausea, abdominal pain |
| Serious Side Effects | Depression, significant weight loss | Hepatotoxicity, leukopenia, interstitial pneumonitis | Myopathy, bone marrow suppression, toxicity in renal failure |
| Monitoring Required | Weight monitoring, mental health assessment | LFTs, CBC (every 2–4 weeks initially); chest imaging if ILD suspected | CBC, renal/liver function tests, CPK if muscle symptoms present |

| Parameter | Apremilast | Iguratimod | Colchicine |
|---|---|---|---|
| Contraindications | Severe depression, underweight patients | Pregnancy, liver disease, and advanced ILD | Severe renal/hepatic dysfunction, concurrent CYP3A4 inhibitors |
| Dose and Administration | 30 mg twice daily (with 5-day titration) | 25 mg twice daily | 0.6–1.2 mg/day (lower doses in elderly or renal impairment) |
| Drug Interactions | Minimal (few CYP interactions) | Additive hepatotoxicity with MTX | Major: Statins, CYP3A4/PGP inhibitors (e.g., macrolides) |
| Key Limitation | GI intolerance, modest efficacy | Limited approval outside Asia, overlap toxicity with MTX | Narrow therapeutic window, GI toxicity, drug interactions |

*CBC: complete blood count; CTD-ILD: connective tissue disorder associated-interstitial lung disease; FMF: familial mediterranean fever; IL-1β: interleukin 1β; LFT: liver function test; NF-κB: nuclear factor-kappa B; PDE4: 4hosphodiesterase 4*

## Conclusion

Apremilast, Iguratimod, and Colchicine represent a diverse array of oral agents with unique mechanisms and distinct clinical niches in rheumatology. While not as potent as biologics, their ease of administration, cost-effectiveness, and suitability in milder cases or resource-limited settings make them valuable tools in the rheumatologist's armamentarium. Careful patient selection, monitoring, and awareness of their limitations are key to maximising their therapeutic benefit.

# URATE LOWERING AGENTS

*Arun Kumar Kedia*

Gout results from either overproduction or underexcretion of urate. While treatment of acute gouty arthritis requires anti-inflammatory drugs, chronic gout requires urate-lowering therapy (ULT) in specific scenarios. This chapter covers various agents available to lower serum uric acid levels.

## URICOSTATIC AGENTS

These drugs inhibit the enzyme Xanthine Oxidase, thereby reducing uric acid production.

### Allopurinol

Allopurinol is a competitive inhibitor of xanthine oxidase (XO).

***Advantages:*** It has a long safety and efficacy record with positive results in patients with cardiovascular disease. Hence, it is the preferred ULT, endorsed by the guidelines.

***Dose:*** It is recommended to start with a dose of 100 mg daily, titrating up slowly every 2–4 weeks until the target serum uric acid (SUA) concentration is achieved, with a maximum daily dose of 800 mg. Patients with chronic kidney disease (CKD) may be started on a lower dose of medication.

***Adverse effects:*** Common side effects include gastrointestinal discomfort and skin rash. Serious adverse effects include severe cutaneous adverse reactions (SCAR), including drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and allopurinol hypersensitivity syndrome

(AIH). AIH is usually seen during the first 2 months of therapy, with advanced age, renal dysfunction, and the presence of the HLA-B*5,801 variant as risk factors. Hence, the 2020 American College of Rheumatology (ACR) guidelines conditionally recommend testing for the HLA-B*5,801 allele before initiating allopurinol in patients of Han Chinese, Korean, Thai, and African descent, as these populations have the highest prevalence of the gene.

### Febuxostat

Febuxostat is a nonpurine, noncompetitive inhibitor of Xanthine oxidoreductase (XOR).

***Dose:*** The usual starting dose is 40 mg daily, with an uptitration to a maximum daily dose of 80-120 mg. Even though it has demonstrated superiority over allopurinol for efficacy and tolerability, it has the disadvantage of an increased cardiovascular disease risk. The adverse effect profile and the high cost of febuxostat make allopurinol the preferred choice over febuxostat, according to the ACR 2020 guidelines.

***Contraindications:*** It is contraindicated in patients on azathioprine or mercaptopurine. Xanthine oxidase inhibition increases concentrations of azathioprine and mercaptopurine, resulting in profound myelosuppression.

### Topiroxostat

It is a non-competitive inhibitor of XOR.

***Dose:*** It is started at a dose of 40-60 mg per day in two divided doses and uptitrated as required. The maximum dose is 80 mg twice daily.

It is safe and offers both cardiovascular and renal benefits, making it a viable alternative to allopurinol and febuxostat.

## URICOSURIC AGENTS

These agents inhibit the uric acid transporters in the kidneys, thereby increasing the excretion of uric acid in the urine. They are contraindicated in patients with urate nephrolithiasis and are only helpful when urinary uric acid excretion is less than 800 mg/day.

### Benzbromarone

It is a non-selective uricosuric agent that lowers SUA by inhibiting Urate Transporter 1 (URAT1), with a lesser effect on Glucose Transporter 9 (GLUT9), Organic Anion Transporter 1 (OAT1), and OAT3 transporters. While the efficacy is comparable to that of allopurinol, its clinical use is limited by its relatively high incidence of hepatotoxicity.

### Probenecid

It lowers urate primarily by inhibiting URAT1 and other anion transporters (OAT1, OAT3, and GLUT9).

***Indications:*** It can be used as a monotherapy in patients who cannot tolerate XOIs or in combination for those who do not achieve the target SUA after XOI monotherapy.

***Dose:*** Start with 500 mg once or twice daily, and gradually titrate to a maximum dose of 2 g per day to achieve the target SUA.

***Contraindications:*** Stage 3 CKD and beyond.

***Major adverse effects:*** Urolithiasis and potential drug-drug interactions. Due to its non-selectivity, it alters the renal clearance of other medications, such as penicillin, furosemide, and methotrexate.

***Indication:*** It is recommended as a second-line agent in the management of gout due to the risk of urolithiasis, drug-drug interactions, and lower potency than other ULTs.

### Lesinurad

It was the first selective urate reabsorption inhibitor (SURI) and was usually administered as a 200 mg daily dose in combination with an XOI. It received FDA approval in 2015, but production was discontinued by the manufacturer in 2019.

### Dotinurad

It is a highly selective URAT1 inhibitor and effective uricosuric agent available only in Japan that appears to be equivalent to benzbromarone and febuxostat in overall uric acid-lowering ability. It is being evaluated for possible approval in the US and Europe.

### Sulfinpyrazone

It lowers SUA by inhibiting URAT1. The manufacturer discontinued Sulfinpyrazone.

## URICASES

These drugs convert uric acid to the water-soluble allantoin, making it readily excretable by the kidneys.

*Indications:* Chronic gout inadequately controlled by XOIs or uricosuric agents alone. They are suitable for cases of intractable hyperuricemia having two or more gout attacks annually while on therapy, or persistent subcutaneous tophi unresponsive to the maximum dosages of conventional treatment.

## Rasburicase

It is the prototypical recombinant uricase, approved for the treatment of hyperuricemia in malignancy and tumour lysis syndrome. It carries a warning for anaphylaxis and methaemoglobinemia. Rasburicase has a potent and rapid urate-lowering effect.

*Disadvantages*: It is immunogenic with the potential for the development of antidrug antibodies (ADA) in many patients. Repeat courses are not recommended due to the fear of anaphylaxis. It is not a preferred agent for long-term management of gout.

## Pegloticase

It is a recombinant uricase conjugated with polyethylene glycol (PEG) approved for use in severe refractory gout. The 2020 ACR guidelines recommend pegloticase for patients who continue to have frequent flares or nonresolving tophi despite compliance with maximally tolerated conventional therapies. Unlike most other ULT, it does not require dose adjustment in renal dysfunction.

*Dose*: The recommended dose is 8 mg intravenously every 2 weeks.

*Disadvantages*: The limitations of pegloticase therapy include the requirement for twice-monthly intravenous infusions, high cost, infusion reactions (including anaphylaxis), incompatibility in patients with glucose-6-phosphate dehydrogenase deficiency, the development of ADA, and a loss of urate-lowering efficacy.

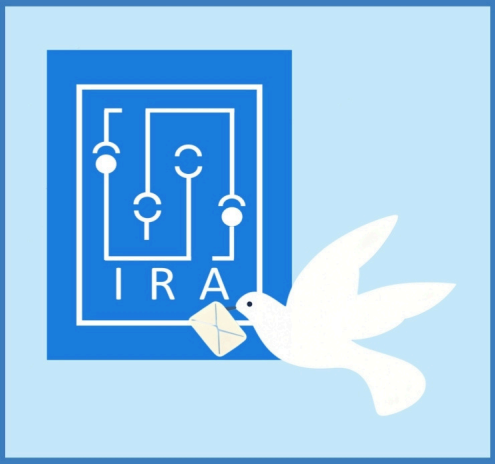
***Precautions:*** This drug needs discontinuation if pre-infusion SUA is greater than 6 mg/dL. Folic acid supplementation should be initiated at least four weeks before the start of therapy. Other uric acid-lowering medications should be discontinued. Monitoring uric acid serum levels before every infusion is advisable. Patients should be premedicated with antihistamines and corticosteroids.

Few molecules are in the preclinical phase or have undergone phase 1 and 2 trials.

***Summary of urate-lowering therapies***

| Drug class | Uricostatics | Uricosurics | Uricases |
|---|---|---|---|
| Mechanism of Action | Xanthine oxidase inhibition | Interferes with uric acid reabsorption | Convert uric acid to water-soluble allantoin |
| Examples | Allopurinol, Febuxostat | Probenecid, Lesinurad Benzbromarone | Pegloticase |
| Indications | Usually, first-line therapy for chronic gout | Second-line therapy for those intolerant to XOI or when the target is not achieved with XOI alone. | Refractory gout with frequent flares and tophi not responding adequately to conventional drugs |
| Precautions and contraindications | Hypersensitivity reactions, esp. allopurinol | Uric acid stones, CKD stage 3 or greater | Infusion reactions Costly |
| Future molecules in the pipeline | LC350189 NC-2500 TMX-049 | ABP-671, D-0120 AR-882, NC-2700 Verinurad | ALLN-346 SEL-212, PRX-115 HZN-007, HZN-003 |

*XOI: xanthine oxidase inhibitor; CKD: chronic kidney disease*

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